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13. ABSTRACT

At the present time the practice of rheumatology continues to rely heavily upon the clinical acumen of the physician, however, intensive research in many diverse fields most notably immunology, biochemistry, and virology, has begun to provide some insight into the pathophysiology of many of these disorders and have afforded the clinician with an increasing number of laboratory parameters useful in the diagnosis and management of many rheumatic conditions.

This issue of Present Concepts reviews several clinical, immunological, and investigational aspects of rheumatology. The titles of the articles define the scope of the symposium. They are: "Chronic virus infections and the connective tissue diseases", "Complement in human disease", "The seropathology of rheumatoid disease", "Myopathy in the collagen diseases", "Juvenile rheumatoid arthritis", "Antinuclear antibodies(ANA)", "Clinical aspects of Sjögren's syndrome", "Pseudogout", and "Cryopathies".

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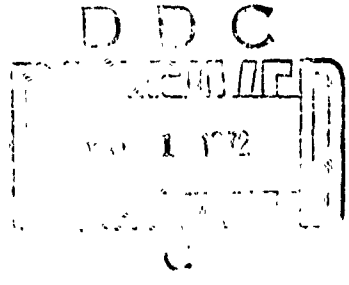

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PRESENT CONCEPTS IN INTERNAL MEDICINE
VOLUME IV *July 1971* Number 7

RHEUMATOLOGY SYMPOSIUM

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FOREWORD

The medical subspecialty of rheumatology deals predominantly with "incurable" diseases for which only limited forms of therapy are currently available. It is unlikely that major therapeutic advances will occur prior to obtaining a better understanding of the etiologies of these disorders. At the present time the practice of rheumatology continues to rely heavily upon the clinical acumen of the physician, however, intensive research in many diverse fields, most notably immunology, biochemistry, and virology, have begun to provide some insight into the pathophysiology of many of these disorders and have afforded the clinician with an increasing number of laboratory parameters useful in the diagnosis and management of many rheumatic conditions.

This issue of *Present Concepts* reviews several clinical, immunological, and investigational aspects of rheumatology. Several papers have come from the Hospital for Special Surgery, Cornell Medical Center, where Doctors Phillips, Lightfoot, Kagen and Lockshin are members of the medical staff, and Doctor Christian is the Physician-in-Chief. Doctor Rothfield is on the the medical faculty of the University of Connecticut School of Medicine. Doctor Jacobs is a practicing pediatric rheumatologist at the Babies Hospital of the Columbia-Presbyterian Medical Center and Doctor Hughes is with the Department of Medicine of the Royal Postgraduate Medical School in London. Major Chier is presently a Fellow in Rheumatology at Letterman. We are indebted to this group of authors for generously contributing to this symposium. It is hoped that the topics presented will be of interest to the general internist as well as demonstrate the increasing spectrum of disorders that are of interest to rheumatologists.

MAJ SELWYN A. COHEN, MC
Guest Editor

. . . The author is frequently asked in giving a talk to make it "practical" and not too "theoretical." By "practical" is usually meant "therapeutic"; by "theoretical" is usually meant "fundamental." The author has no patience with such a philosophy. One cannot possibly practice good and not understand the fundamentals underlying therapy. Few if any rules for therapy are more than 90 per cent correct. If one does not understand the fundamentals, one does more harm in the 10 per cent of instances to which the rules do not apply than one does good in the 90 per cent to which they do apply.

—Fuller Albright

Editor's Note: These words I have in my notes. They have been printed in *Cecil-Loeb Textbook of Medicine*, and quoted numerous other times. The last time I think I saw them in print, I was thumbing through *Annals of Internal Medicine* (August 1970). E.A.C.

EDITORIAL

Charles L. Christian, M.D.

Physician-in-Chief
The Hospital for Special Surgery, Cornell College of Medicine, New York

This volume of *Present Concepts of Internal Medicine* reviews a part of the spectrum of rheumatic disease. As with all subspecialties, the boundaries of Rheumatology are poorly defined. They overlap extensively other subdisciplines of internal medicine, as well as the fields of orthopedic surgery, neurology, and rehabilitation medicine. The multisystemic manifestations of a syndrome, like systemic lupus erythematosus (SLE), highlight the varied clinical skills that are requisite for management.

To date there has been no formalization of training or certification in Rheumatology — most consultants in this area are broadly trained internists with special, but not exclusive, interest in this field. The American Board of Internal Medicine, however, has announced its intention to examine Diplomats of the Board who wish additional certification in Rheumatology (*Ann Intern Med* 74:434, 1971). Under the current proposal, candidates wishing such certification will be eligible after completing two years of subspecialty training. It remains to be seen how many physicians now practicing as consultants will seek such certification.

The research disciplines that are relevant to the study of rheumatic disease include all fields of biological science. Although some of the rheumatic syndromes are clearly metabolic problems, i.e. gout and alkaptonuria, the pathogenetic bases for most types of chronic rheumatism are not known. As sections in this volume emphasize, there are prominent immunological abberations in disorders like SLE and rheumatoid arthritis and new concepts, more than new data, have reawakened interest in microbial hypotheses for the pathogenesis of such syndromes. Even though the individual connective tissue syndromes seem distinct in their classical forms, there is much in common and there is reasonable promise that elucidation of the pathogenesis of one syndrome will also have relevance to

the others. In common with most diseases of unknown etiology, there is evidence that multiple factors participate in pathogenesis. The type of scientific inquiry applied to the study of neoplasia — involving the interrelationship of genetic, immunological and virologic factors — seems equally promising for syndromes such as SLE.

The Rheumatologist lacks a "cure" for most that he treats. To the inquiring physician, the resulting frustration is a sustained stimulation to gain new information regarding the etiology and pathogenesis of rheumatic disease.

CHRONIC VIRUS INFECTION AND THE CONNECTIVE TISSUE DISEASES*

Paul E. Phillips, M.D.†

The idea that the connective tissue diseases might have an infectious basis is not new. In the 1930s rheumatoid arthritis was commonly called "chronic infectious arthritis"—at that time infection was the recognised cause of inflammation. With the discovery of rheumatoid factor and other autoantibodies in the 1940s and 1950s, the connective tissue diseases became known as autoimmune diseases. While efforts focused on unravelling the nature and mode of action of autoantibodies, the underlying causes were still elusive. Thus the idea that the autoimmune phenomena might be secondary to environmental causes received another look. The possible role of chronic virus infection has received considerable attention, primarily because of the recent increase in understanding of such infections in animals and man.

Virus diseases are usually thought of as acute infections, with virus multiplication leading directly to cell damage and disease. Within a couple of weeks, the host responds immunologically with both circulating antibody and cellular immunity, which lead to virus elimination. Clinical recovery follows and lifelong immunity usually results. The common virus diseases of childhood —measles, chicken pox and rubella— are typical examples of usually acute virus infections. However, it has become apparent that this outline is too simple because, first, clinical signs of such viral illnesses may not occur until the host responds immunologically. For instance, rash commonly appears at the same time as circulating antibody, thus the host immune response may itself be partially responsible for tissue damage. Secondly, the virus infection may alter the immunologic status of the host; e.g., the depression

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of tuberculin skin test reactivity in measles or, conversely, the enhanced immune responses seen in some virus-infected animals. Thirdly, one mechanism of lifelong immunity may actually be the persistence of the virus or its antigens in the host.

The more recently recognized chronic virus infections (also known as slow, latent, temperate or persistent) may not be accompanied by clinical signs. In animals these viruses are often transmitted vertically from mother to fetus, with virus replication proceeding asymptomatically. The crucial difference between these viruses and an ordinary acute virus infection is that the virus is not eliminated by the host immune response. In animals, the host may continue to respond immunologically to the persistent virus, and clinical disease then results primarily from immunological reactions with the virus or its antigens in the host's tissues. There may be no apparent disease for a time, then it may be mild to severe with an episodic or progressive course; the exact pattern with a particular virus seems to depend on the nature of the host immune response to chronic infection, which in turn appears to be largely controlled by genetic factors. Thus genetic susceptibility probably determines in part whether chronic virus infection occurs, and its subsequent manifestations.

In man, herpes simplex and herpes zoster are well-known examples of chronic virus infections, which result in episodic acute disease. TABLE I. Kuru and Jakob-Creutzfeldt disease are progressive encephalopathies of the spongiform type, and have been transmitted to other primates. /1/ Also progressive is subacute sclerosing panencephalitis, which was thought to be of viral etiology by its discoverer Dawson in the 1930s. Not until recently was this disease actually shown to be a chronic measles infection (although another virus may be involved as well). /2,3/ Persistence of the virus of serum hepatitis, manifest as Australian antigen, can be asymptomatic. Indirect evidence suggests that neoplasia in man may result from virus persistence. /4/

Research with chronic virus infections in animals has been instrumental in enlarging our understanding in this area and in its application to human disease. TABLE I. Examples include scrapie, a transmissible neurologic disease of sheep, which is histopathologically similar to kuru in man. /1/ The RNA leukemia-sarcoma viruses, best studied in mice and chickens,

are models of vertically transmitted chronic infection with pathogenetic implications for similar human disorders. /4/ Aleutian disease of mink, lymphocytic choriomeningitis (LCM) in mice, and New Zealand mouse disease are important models for the connective tissue diseases, because in these tissue injury is mediated by immunologic processes, particularly by immune complexes. /1,5/

TABLE I

SOME CHRONIC VIRUS INFECTIONS

In man

- Herpes simplex (fever blisters, cold sores)
- Herpes zoster (shingles)
- Kuru
- Jakob-Creutzfeldt presenile dementia
- Subacute sclerosing panencephalitis (SSPE)
- Australia antigen viral hepatitis
- (?) Neoplasia
- (??) Connective tissue diseases

In animals

- Scrapie in sheep
- Mouse and avian leukemia - sarcoma
- Aleutian disease (AD) of mink
- Lymphocytic choriomeningitis (LCM) in mice
- Autoimmune disease in NZB and (?) NZB/W hybrid mouse

The classic disease caused by immune complexes is serum sickness (where host antibody combines with the foreign serum protein, is deposited with complement in the kidney, and glomerulonephritis results). In human systemic lupus erythematosus (SLE), DNA and anti-DNA antibody immune complexes are thought to be an important pathogenetic mechanism.* Similarly, in the nephritis of Aleutian disease and LCM, virus or viral antigens are involved in the formation of the immune complexes. In addition, viral antigens in the tissues are subject to immunologic attack by the host, with resulting tissue damage. /1,5/

In the SLE-like disease of New Zealand mice, a close correlation has been shown between the appearance of a murine leukemia virus antigen in the circulation and the onset of

*Dr. Cohen discusses these on pages 528,530.

Coombs' positive hemolytic anemia. The subsequent appearance of antibody to this antigen correlates well with the disappearance of the latter from the circulation (presumably via the formation of immune complexes), the appearance of immune complex-type nephritis and proteinuria, leading to death of the mice. /1,6/ Thus, the SLE-like disease of these mice seems to result from their immunologic response to chronic infection with murine leukemia virus. However, others /1,5/ have shown that these mice are immunologically hyperreactive to a variety of other antigens. Furthermore, since all strains of mice are probably chronically infected with leukemia virus /4/ and usually without auto-immune manifestations, one has to invoke a genetic basis for the hyperreactivity of this inbred strain. Similarly, in many of the other animal models of chronic virus infection leading to immunologically mediated disease, a genetic predisposition seems essential to explain why only certain strains of animals are affected. /1,5/

While these animal models suggest that similar mechanisms may be involved in the human connective tissue diseases, the actual evidence for chronic virus infection here is at best circumstantial. In SLE, microtubular inclusions have been found in renal glomerular endothelium with the electron microscope. /7/ These inclusions appear similar to those caused by measles in subacute sclerosing panencephalitis /2/ and thus have been termed "paramyxovirus-like". Although they are most numerous in SLE, they have also been found in a variety of unrelated diseases, and thus are not specific for SLE. Morphologically they differ somewhat from the known appearance of the paramyxoviruses (TABLE II) and attempts to identify their viral nature by immunofluorescent and other techniques have so far been unsuccessful. /8/ Similarly, virus isolation studies in SLE, including attempts to culture these inclusions, have been negative (our own experience is shown in TABLE III). Thus the role of these inclusions in the pathogenesis of SLE, as well as their actual nature, remains unclear. /8,1/

Likewise, attempts to incriminate a specific virus by showing elevated titers of antibody to it in the serum of SLE patients have not succeeded. Measles, parainfluenza, rubella, Epstein-Barr virus antibody levels, and others, are significantly elevated in SLE compared to control subjects. TABLE IV. While yet other virus antibodies have not been significantly elevated in SLE, the numbers of patients studied have often been small and the methods used for measuring some of these antibodies relatively insensitive. /10-12, 1/ Our own studies indicate

TABLE II

PARAMYXOVIRUS AND "VIRUS-LIKE" MICROTUPULAR INCLUSIONS

Inclusion	In cytoplasm only	Membrane bound	Tightly coiled	Diameter of tubule Outer	Inner
				⇐Angstrom⇒	
Measles	0	0	0	180(140-200)	50
SSPE*	0	0	0	160(150-200)	50
SLE†	+	±	+	230(190-250)	80

*Subacute sclerosing panencephalitis

†Systemic lupus erythematosus

TABLE III

VIRUS ISOLATION STUDIES OF TISSUE CULTURES FROM SLE PATIENTS

Successful growth:	10/13 specimens, 9/10 patients.		
Mean duration:	5.4 mo. (1-12).		
No evidence of virus by:			
Cytopathic effect	10 strains	Hemagglutinin	3 strains
Cocultivation	3	Hemadsorption	1
Cell fusion	2	Interference	2

TABLE IV

VIRUS ANTIBODY ELEVATIONS IN SLE

Measles	Reovirus type 2
Parainfluenza type 1-3	Infectious bronchitis OC 43
Respiratory syncytial	Herpes simplex
Rubella	EB virus

that at least the measles and parainfluenza type 1 antibody elevations reflect the hypergammaglobulinemia commonly found in SLE. This and the multiplicity of the virus antibody elevations suggest they are a result (rather than the cause) of the immunologic hyperreactivity which is characteristic of SLE.

Turning to rheumatoid arthritis, no animal model caused by chronic virus infection is known. However, there has been increasing evidence for the formation of immune complexes in involved joints. Rheumatoid factor, itself an autoantibody (against altered IgG), appears to be involved but the initial antigenic stimulus in this chain of events is still unclear. Chronic microbial infection could provide such a stimulus and a variety of isolates have been obtained from rheumatoid synovia over the years, including diphtheroid bacilli, mycoplasma (PPLO) and other less well-characterized agents. /1/ Since Koch's postulates cannot be fulfilled for these isolates (i.e. they cannot be inoculated into human subjects), their significance can only be assessed by less direct methods and remains unclear at present. The particular problems in evaluating such isolates are to determine (1) that they are not contaminants introduced during the usually complex laboratory manipulations, and if not, (2) that they are pathogenic and not "passengers" or secondary invaders of already damaged synovia. Reproducibility of results in different laboratories is a third problem. More recently Grayzel and Beck /13/ and others /1,5/ have shown that rheumatoid synovial cells are resistant to superinfection with Newcastle disease and rubella viruses, and that the resistance may be transmissible in vivo to rabbit synovial cells. In other systems, such resistance has been found to be due to an otherwise inapparent infection with another virus, thus this work may be the first clue of such an infection in rheumatoid synovial cells. However, metabolic differences have also been found between rheumatoid and normal synovial cells and, while these might result from an inapparent virus infection, Castor's work /14/ suggests that the difference is due to a peptide "activator" substance. Such metabolic differences could be responsible for the resistance found in rheumatoid cells. Many other attempts at isolating viruses from rheumatoid synovia have been negative, including our own with over 60 patients. /1,5/ Electron microscopic and serologic studies in RA have been unrewarding to date, /1/ thus there is no firm evidence at present that chronic infection, viral or other microbial, plays a role in the pathogenesis of rheumatoid arthritis.

In the rarer connective tissue diseases —— dermatomyositis, scleroderma and polyarteritis nodosa —— there had been little evidence to suggest a virus etiology, although certain animal models were suggestive. /1/ However, Gocke et al /15/ recently described persistence of Australian antigen in certain patients with typical polyarteritis, with strong evidence for the pathogenetic role of immune complexes containing Australian antigen and antibody. Thus, it seems likely that some cases of this disease are caused by a chronic infection with the virus of serum hepatitis. This discovery should encourage a continued examination of the possible role of chronic virus infection in the connective tissue diseases.

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COMPLEMENT IN HUMAN DISEASE

MAJ S. A. Cohen, MC

The complement (C) system has been clearly implicated in the pathogenesis of many human and experimental diseases./1,2/ Increasing availability of component and total hemolytic complement assays have provided clinicians with useful parameters in the diagnosis and treatment of many of these disorders. A review of disease states involving abnormalities of the C system forms the basis of this article. The abnormal C level at any given time reflects both catabolic and synthetic rates of individual components. However, measurement of the metabolism of these components is presently available only at a few research laboratories and this paper will deal mainly with those laboratory determinations readily available, i.e., total hemolytic C and C3 levels.

The C* system consists of a group of serum proteins that interact sequentially to mediate certain of the effects of antigen-antibody reactions. This activation of the C system is initiated by the union of an appropriate antibody either with soluble antigen or with an antigen located on the surface of such target cells as erythrocytes, tumor cells, bacteria or protozoa. Many antigen-antibody complexes are inert in a biological sense and their ability to cause tissue damage is dependent upon their ability to activate the C system. This, in turn, can lead to several important biological phenomena: attraction of polymorphonuclear leukocytes, increased membrane permeability, adherence of antigen-antibody complexes to erythrocytes, polymorphonuclear leukocytes, or platelets (immune adherence), increased phagocytosis by polymorphonuclear leukocytes, and production of a defect in the target cell membrane which leads to osmotic lysis and cell death.

*C represents 'complement". The nomenclature for the components of the C system conforms to that agreed upon by World Health Organization, 1968, and are designated C1, C2, C3, etc. The activated state of a component is signified by a bar above the number, e.g., $\overline{C1}$.

(The membrane defect, when visualized by electron microscopy, appears to be a hole 103Å in diameter, and is identical in all types of cells. /3/) The effect of C activation might therefore be hemolysis, killing of bacteria, lysis of tumor cells, or it might be to enhance tissue inflammation in an area of antigen-antibody complex deposition.

The standard laboratory procedure used to measure C levels is determination of the "total hemolytic complement" (CH_{50}). This analysis utilizes the ability of the activated C system, under appropriate circumstances, to lyse sensitized erythrocytes; specifically, it measures the ability of a test fluid to lyse 50 percent of a standarized suspension of sheep erythrocytes coated with rabbit antisheep erythrocyte antibodies in absence of complement. Test serum is then added and a determination is made of the greatest dilution which will cause 50 percent cell lysis. The CH_{50} is inversely proportional to this dilution and is a functional measure of the integrity of the entire C system. As will be discussed below, this system is actually composed of nine components plus three inhibitors or activators and a low CH_{50} could reflect decreased activity of a single component, reduction in the activity of multiple components, or an abnormality of an inhibitor. Functional and physical evaluation of many individual components are also now available.

The activation of the C system begins with the binding of an antigen-antibody complex to C1. Figure 1. This component consists of three subunits, C1qrs, and it is actually C1q that binds to the immune complex. C1s, a proesterase, is converted to an active esterase ($\overline{C1}$) by the immune complex. /Normal people have an inhibitor (C1 INH) of this esterase in their serum/ $\overline{C1}$ then acts on C4 and C2 converting these components into the $\overline{C142}$ complex called C3 convertase, which splits C3 into fragments. Complexes in the $\overline{C142}$ state have biological activity and react in immune adherence, undergo enhanced phagocytosis and are associated with the generation of a potent histamine liberator anaphylatoxin. The remaining components are added in a poorly understood manner. All nine components are needed for erythrocyte lysis.

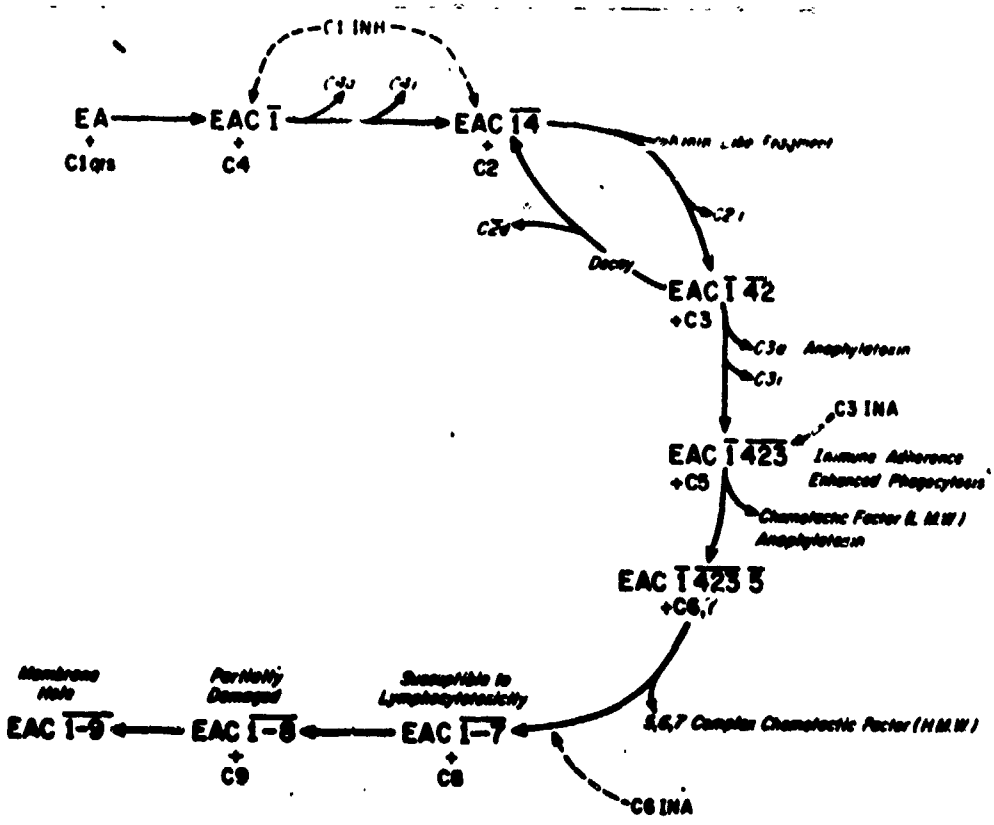


Fig. 1. The reactions of the complement system. This scheme appears a number of places in the literature, although this diagram is accredited to Ruddy S, Austen KF: Inherited abnormalities of the complement system in man. *Prog Med Gen* 7:69-95, 1970. EA represents an erythrocyte-antibody complex.

INBORN ERRORS

Conditions listed in TABLE I represent intrinsic abnormalities of the C system. Hereditary angioneurotic edema (HAE) has been the most intensively studied of the inborn errors and is described below. The remaining abnormalities are mentioned only briefly.

Hereditary Angioneurotic Edema

Early in the C sequence activated $\overline{C1}$ (an esterase) reacts with C4 to form $\overline{C14}$. In normal people there is a circulating inhibitor (C1 INH) of this $\overline{C1}$ esterase. The serum abnormality

TABLE I

INBORN ERRORS*

Hereditary angioneurotic edema
C2 deficiency
Partial deficiency of C3
C1q deficiency with thymic aplasia
C1q deficiency with impaired immunoglobulin synthesis
Defective C5 in a familial abnormality of phagocytosis

unique to HAE is the functional absence of this C1 esterase inhibitor. Figure 2. In some families this protein is absent from the sera, while in others it is present in normal amounts, but is nonfunctional. The laboratory diagnosis can be made by screening for the inhibitor (C1 INH) itself or by demonstrating low C4 and C2 levels. The natural substrates of the uninhibited C1. Components which are beyond the C2 step do not seem to be involved. CH_{50} is usually depressed during the acute attack of angioneurotic edema, but occasionally is normal.

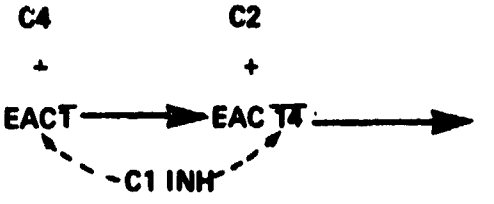


Fig. 2. Hereditary angioneurotic edema. C1 INH is the normal inhibitor of the first component of complement. In HAE this Protein may or may not be present. If present, it is functionally inactive.

This genetic abnormality is transmitted as an autosomal dominant with incomplete penetrance. Clinical symptoms consist of attacks of subepithelial edema involving the skin, mucosa of the GI tract (which may cause intestinal obstruction), and mucosa of the upper respiratory tract. Laryngeal edema due to upper respiratory tract involvement is the leading cause of death. Emotional stress and trauma often precede the acute attack, but obvious precipitating factors are absent in most episodes. The edema usually subsides spontaneously within 24-48 hours and at the present time only symptomatic therapy is available, along with careful observation for the appearance of laryngeal edema. The recent description /5/ of this

syndrome occurring for the first time in a 61-year-old woman with a negative family history demonstrates that HAE should be considered even in elderly patients without a positive family history who develop skin and mucosa edema.

Other Inborn Errors

C2 deficiency, transmitted as an autosomal recessive characteristic, has been reported in several families. The concentrations of C2 in homozygous deficient sera are less than five percent of normal; in heterozygous deficient sera they vary between 30 to 70 percent of normal. /2,6/ No clinical abnormalities have been detected in these families. A partial familial deficiency of C3 has also been noted without any apparent clinical manifestations. /2,7/

Low C1q levels have also been detected in a variety of hypogammaglobulinemic syndromes and recently a direct correlation between serum levels of IgG and C1q has been demonstrated. /8/ A syndrome of recurrent gram negative infections in infants has been associated with a familial deficiency in C5 function. /9/ These patients have a normal CH_{50} but apparently have a defect of C5 which impairs its ability to enhance the phagocytosis of certain antigens, but not of others, and leaves intact its antigenicity and its function in immune hemolysis. Control of the infections has followed plasma transfusions.

ACQUIRED ABNORMALITIES

In the situations presented below, abnormalities in C level are secondary manifestations of an underlying disease process. Elevated serum C has been reported in ulcerative colitis, acute rheumatic fever, myocardial infarction, gout, rheumatoid arthritis, thyroiditis and many other disease entities. Several C components are acute phase reactants and are elevated in any inflammatory condition. An elevated C level is, therefore, a non-specific finding common to a large number of disease disorders. Depressed C levels are considerably less common and have been detected in the diseases listed in TABLE II. The depression may be due to increased utilization of C (e.g., serum sickness, cold agglutinin

disease, mixed cryoglobulinemia), decreased synthesis of complement (e.g., liver disease), or due to still unexplained mechanisms (e.g., macroglobulinemia).

TABLE II

ACQUIRED ABNORMALITIES

Serum sickness
Acute post-streptococcal glomerulonephritis
Systemic lupus erythematosus
Autoimmune hemolytic anemia
Rheumatoid synovial effusion
Progressive glomerulonephritis of childhood
Cryoglobulinemia
Subacute bacterial endocarditis with renal disease
Macroglobulinemia
Renal transplant rejection
Myasthenia gravis
Chronic glomerulonephritis
Malaria
Severe liver disease

Serum Sickness

Human serum sickness closely simulates "one shot experimental serum sickness". In classic one-shot serum sickness a single large dose of foreign serum or protein is injected. Figure 3 illustrates the serological events that will take place in the subject. The antigen level in the serum will first slowly decrease, due to non-immune catabolism of circulating free antigen, followed by a phase of rapid loss just preceding the appearance of free circulating antibody. As the antibody forms it first combines with the antigen in extreme antigen excess with resultant formation of small soluble complexes capable of remaining in the circulation as indicated by the complex line. As the amount of antibody formed increases, the antigen-antibody complexes become larger and are rapidly removed. Coincidental with the presence of antigen-antibody complexes in the circulation, there is a fall in serum C and the appearance of acute inflammatory lesions

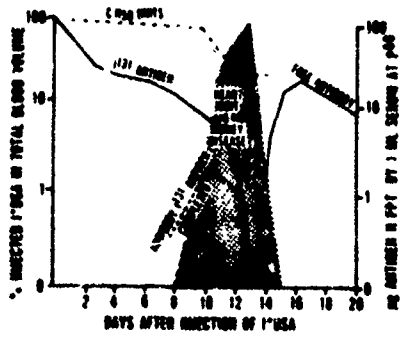


Fig. 3. Serum sickness. The elimination of injected ^{131}I-labeled antigen. Serum sickness (shaded area) occurs following the appearance of soluble antigen-antibody complexes and resolves following their disappearance. *(Permission to reproduce was kindly granted by Charles L. Christian, M.D.)*

in the kidneys, heart, arteries and joints. The subject at this time has clinical serum sickness which usually resolves without any sequelae. Using immunofluorescent techniques, antigen, antibody and C can be demonstrated in the cardiovascular and renal lesions during the acute episode, but with the elimination of all immune complexes from the system, the inflammatory lesions in all sites rapidly resolve with minimal, if any, permanent changes remaining. In this situation low C seems clearly to be due to activation by the circulating antigen-antibody complex and deposition of its components in the body tissue.

Acute Poststreptococcal Glomerulonephritis

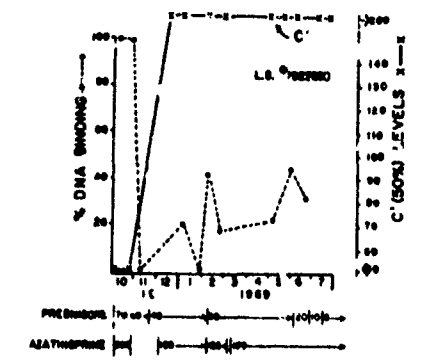
Complement is usually low in acute poststreptococcal glomerulonephritis (AGN). That this disease is caused by circulating antigen-antibody complexes is suggested by its similarity with acute serum sickness nephritis. A delay of seven to nine days is seen following the administration of foreign protein and the onset of serum sickness; similarly, there is an interval following streptococcal infection and the onset of AGN. At the first detection of renal abnormality, in both situations, there is a decreased serum C. /11/ Gamma globulin and C3 globulin are found within the glomeruli as discrete fine nodular deposits adjacent to the glomerular basement membrane in both diseases. Type 12 streptococcal products have also been detected in the same area in AGN /12/ and recently antibodies against streptococcal antigen have been eluted from glomeruli of rats with poststreptococcal glomerulonephritis /13/. This information suggests that

antistreptococcal antibodies and streptococcal antigen combined with C have pathogenetic importance in acute poststreptococcal glomerulonephritis.

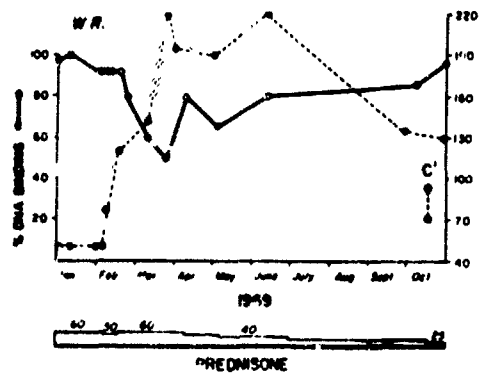
Systemic Lupus Erythematosus

It is now widely appreciated that C levels are often depressed in systemic lupus erythematosus. /14/ In most cases this depression correlates best with activity of lupus nephritis, and probably represents C fixation by circulating immune complexes that are subsequently deposited along the renal glomerular basement membrane. Recent studies have suggested that the DNA-anti DNA immune system is of particular significance in this disease; the role that other specific antigen-antibody complexes play in the pathogenesis of lupus nephritis remains unclear at the present time. The evidence that lupus nephritis represents an "immune complex" disease is as follows. /15/ (1) Immunoglobulins and C are present in a "lumpy" immunofluorescent pattern similar to that seen in serum sickness as opposed to the linear pattern present in Goodpasture's syndrome caused by antiglomerular basement membrane antibodies. (2) The electron microscopic picture is identical to that seen with serum sickness. (3) Antinuclear antibodies can be eluted from lupus kidneys in concentrations greater than in corresponding sera and anti DNA antibodies have been detected in the eluates. (4) DNA has been demonstrated by immunofluorescence in the deposits within the glomerular basement membrane. (5) Serum C levels are depressed during periods of active nephritis. (6) Antinative DNA antibodies and native DNA have been demonstrated in the serum of patients with lupus nephritis — although they have not yet been detected simultaneously nor in circulating complexes.

Patients with circulating anti DNA antibodies usually become ill after the serum C begins to fall. Complement remains low throughout the period of active nephritis and rises following adequate therapy with corticosteroids or immunosuppressive therapy. The relationships between anti DNA titer (as measured by the sensitive Farr technique) /16/ serum C levels and clinical disease are illustrated in Figure 4A, B, and C.



A



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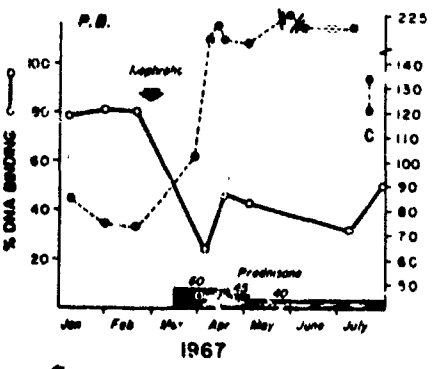

C

Fig. 4, A, B and C. Relationship between C, anti-DNA titers and active SLE. Percent DNA binding represents anti-DNA titer (normal is less than 20 percent). Normal C levels are above 120. Detailed explanation of the parts of the figure is given in the text. ***(Permission to reproduce graphs was kindly granted by Charles L. Christian, M D.)***

The serial studies depicted in Figure 4A are from a patient who presented with severe active lupus nephritis; C levels as represented by the solid line were below 50 (normal is greater than 120), and the DNA binding activity (anti DNA titer) represented by the dotted line was 100 percent (normal is less than 20 percent). After therapy with prednisone and Imuran was instituted, the patient improved, the C rose to normal levels, and DNA binding activity decreased to normal. A similar study appears in Figure 4B. On this graph the dotted line represents serum C levels which was initially quite low and the DNA binding activity which was 100 percent initially is represented by the solid line. This patient was acutely ill when first seen. After therapy was begun, C levels rose to normal, the DNA binding activity decreased, although never to normal levels, and the patient responded clinically. However, the DNA binding activity began to rise again. C level decreased in October 1969 and the patient ultimately had a clinical relapse. That an elevated DNA binding activity and low C level may signify an impending clinical exacerbation of

disease is again illustrated in Figure 4C. This patient was clinically well in January 1967 although 80 percent DNA binding activity (the solid line) was present, as well as a low serum C. Two months later she became grossly nephrotic. On steroid therapy both clinical state and serological abnormalities improved. Studies of this type have suggested that serum C may be a useful guide for evaluating therapy in patients with lupus nephritis and in predicting possible exacerbations of disease activity. It has recently been demonstrated that central nervous system complement titers are depressed in active central nervous system lupus and that this depression is not a reflection of serum values. These data suggest that the neuropsychiatric complications of SLE may be caused, in part, by activation of the C system within the central nervous system. /17/

Autoimmune Hemolytic Anemia

It is currently thought that the attachment of antibody to erythrocyte does not, by itself, produce irreversible damage to the cellular membrane. If this antigen-antibody reaction is followed by fixation of all nine C components, then membrane lesions may be produced leading to the dissolution of the cell. Alternatively, early components of C may become bound to the erythrocyte membrane leading to accelerated clearance of the red blood cell from the circulation. /18/ Cold agglutinin disease and paroxysmal cold hemoglobinuria are well-documented examples of C mediated hemolytic disease and are discussed below and in more detail on pages 585 and 586.

Cold agglutinins have been detected in primary atypical pneumonia, infectious mononucleosis, SLE, lymphoproliferative disorders and in "idiopathic cold agglutinin disease". /19/ The antibody is an IgM anti-I (less often anti-i) which fixes to erythrocytes circulating in superficial blood vessels exposed to the cold. Attachment of the anti-I antibody is a reversible temperature dependent process, being maximal at 0C and weak or absent at 37C; however, the C fixed to the erythrocyte in the cold is not eluted in the warm. A standard Coombs' reagent directed against γglobulin ("γ Coombs' reagent") would thus be non-reactive at 37C (but positive if done in the cold), while a broad specificity or non γCoombs' reagent capable of reacting with C on the erythrocyte would give a positive result. Therapy is directed against the underlying disease process.

Paroxysmal cold hemoglobinuria is an uncommon disorder characterized by sudden passage of hemoglobin in the urine following local or general exposure to cold. An IgG anti-T antibody reacts in the cold with the erythrocyte and binds C1q to the cellular membrane. It is only after the blood temperature has returned to 37C that the remaining C components attach onto the erythrocyte and cause hemolysis. The disease is usually, but not invariably, secondary to lues.

Rheumatoid Synovial Effusions

Synovial fluid from patients with rheumatoid arthritis (RA) contain less C relative to the total synovial fluid protein than do synovial fluids from other forms of arthritis, and the extent of this reduction is proportional to the titer of rheumatoid factor. Inclusions of IgG, IgM, rheumatoid factor, and C have been detected within leukocyte from these hypocomplementemic synovial fluids. /20/ It has been suggested that in patients with RA immune complexes form in the synovial fluid, activate the C system and are then phagocytized by synovial fluid leukocytes. Rheumatoid factor probably attaches to the immune complex and enhances C activation; the nature of the immune complex, however, remains unclear at the present time. /21,22/ (Aggregated IgG is also found in some of these synovial fluids and may be responsible for activation of the C system). Recently, low serum C levels have been detected in a few patients with severe RA. /23/ The seropathology of RA is reviewed in this symposium on pages 537 through 541.

Other Acquired Abnormalities

Progressive glomerulonephritis of childhood /24/ (chronic hypocomplementemic glomerulonephritis) is primarily a disease of adolescent or pre-adolescent girls which is characterized by a slow indolent course marked by episodes of gross hematuria or edema or both, associated frequently with anemia and hypertension. These children have a persistently low C level and IgG and C3 are deposited along the glomerular basement membrane in a lumpy distribution. The renal disease is progressive and does not respond to steroid, immunosuppressive or anticoagulant therapy.

Cryoglobulins may be associated with low C levels and are discussed in detail in this symposium on pages 580 through 584.

Low C levels have been reported in patients with subacute bacterial endocarditis (SBE) and renal involvement, while normal C is the rule in SBE without renal disease. /25/ This may be due to complement fixation by antibody and bacterial antigen resulting in an immune complex nephritis. The glomerulonephritis seen with infected ventriculo-atrial shunts may have a similar pathogenesis. /26/

A recent report /27/ documented that a low serum C level is a common occurrence in macroglobulinemia. The cause for this, as yet, is completely unknown. C levels usually increase at the time of renal transplant rejection and decrease below normal as the rejection episode subsides. It usually remains low for several weeks and finally stabilizes after the rejection crisis has passed. /28/ Patients with myasthenia gravis or chronic glomerulonephritis occasionally have low C levels. The malaria caused by P. falciparum is frequently associated with hypocomplementemia.* Although it is known that malaria infection is accompanied by a marked immunological response by the host, the reason for the low serum C remains unclear at the present. Several C components are synthesized in the liver and severe liver disease may result in a reduction in C activity. /1/

It is becoming clear that abnormalities of the C system are present in many diverse pathological situations and that measurement of total hemolytic complement (CH_{50}) or even quantitation of C components does not necessarily portray an accurate picture of the state of this complicated system. Functional analysis of C components will probably add considerable insight to our understanding of the effects of immune reactions and the contribution of the C system to tissue injury.

*Cohen SA. Observations, 1970-71

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THE SEROPATHOLOGY OF RHEUMATOID DISEASE

Robert W. Lightfoot, Jr., M.D.*

While joint involvement is the most common clinical manifestation of the disease commonly known as rheumatoid arthritis, most patients with this disorder in fact have involvement of many organ systems with a chronic inflammatory process typical of the rheumatoid joint. In some patients extra-articular disease may be sufficiently severe so as to comprise a major threat to health and life. For these reasons it may be preferable to discard the term "rheumatoid arthritis" and replace it with the more appropriate "rheumatoid disease" (RD).

Current speculation favors an infectious etiology for RD. Such a concept is not new. In 1931, Cecil and his collaborators were able to culture streptococci from rheumatoid synovial fluids. Serological studies revealed titers of streptococcal agglutinins in rheumatoid serums to be significantly higher than in the normal population. It was subsequently discovered that rheumatoid serums possessed high titers of antibodies against a variety of bacterial pathogens. The significance of these findings was not appreciated until the discovery of the rheumatoid factor several years later.

In 1940 Waaler reported finding in rheumatoid serums a factor which was capable of agglutinating sheep erythrocytes coated with subagglutinating doses of antibody. This observation was neglected until the report of Rose and his associates in 1948 of the presence of a similar factor in rheumatoid serums. Studies by a number of other investigators have elucidated the nature of this rheumatoid factor.

Rheumatoid factor (RF) has been found to be not one, but a collection of antibody proteins found in the serums of rheumatoid patients in high titer. Classically they are 19S, macroglobulin antibodies of the IgM variety, whose antibody activity appears to be primarily directed toward the human 7S IgG proteins. In this sense rheumatoid factors may be considered to be anti-antibodies. In most patients they

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exhibit some cross reactivity with IgG proteins of other species. Less commonly, such factors may be found in the 7S IgG component of rheumatoid serum, again with antibody activity toward human IgG protein.

Although some evidence indicates reactivity of rheumatoid factors with native unaltered IgG they are known to react preferentially with IgG that has been denatured to some degree. This may vary from a mild steric alteration occurring when IgG antibody reacts with antigen, to the more severe denaturation induced by heating gamma globulin for several minutes at 63 degrees centrigrade.

Tests for rheumatoid factors generally utilize a particulate marker coated with IgG. The particle employed may be a polystyrene latex particle coated with pooled human gamma globulin, a red blood cell tanned with gamma globulin, or an Rh-positive cell sensitized with anti-Rh antibody. In some instances heat-aggregated gamma globulin may be the "particle". In the presence of a positive serum, such particles are agglutinated. The presence of naturally occurring antibacterial antibodies in a serum possessing such an anti-antibody probably explains the high titers of antibacterial agglutinins found in the earlier studies, in which case the bacterium served inadvertently as the particulate marker.

Rheumatoid factors can be demonstrated in 70 to 80 percent of patients with documented RD using the techniques outlined above. A small percentage of rheumatoid factor-negative patients have been shown to possess hidden rheumatoid factors which are revealed by separating their 19S and 7S immunoglobulins with column chromatography. In spite of these and more elaborate methods used, a small number of patients with classical RD exist in whom no rheumatoid factor activity can be demonstrated. Furthermore, there are a number of diseases closely related to RD, such as ankylosing spondylitis, Reiter's syndrome, and juvenile rheumatoid disease, in which rheumatoid factors are usually absent. The presence of rheumatoid factors in an arthritic is not diagnostic of RD, since they are found in from one-third to one-half of patients with related connective tissue diseases such as systemic lupus and scleroderma, and occur with low frequency in normal serums.

The role of rheumatoid factors in pathogenesis is not fully known, but would appear to be negligible. In the RD

joint, phagocytosed complexes of rheumatoid factor and 7S IgG have been found in joint fluid leukocytes, and it is thought that they may represent a potent stimulus to phagocytosis, with attendant release of hydrolases into the joing space. That rheumatoid factors do not play a primary role in disease pathogenesis is suggested by the failure to produce symptoms on transfusion of RF-rich serum into normal volunteers. This contention is supported by the finding of naturally occurring RF in normal persons as well as in a variety of illnesses which bear no clinical similarities to RD. Among such diseases are kala-azar, leprosy, tuberculosis, syphilis, and bacterial endocarditis.

Rheumatoid factors may be found in many conditions characterized by prolonged immunological stress. RF can be induced in laboratory animals by hyperimmunization and are known to occur in low titer in military recruits and bacteriology laboratory personnel prophylactically hyperimmunized. In bacterial endocarditis removal of the immunological stimulus with antibiotic therapy results in disappearance of the rheumatoid factors.

In spite of the nonspecificity of rheumatoid factors for RD and the failure to demonstrate a significant role in pathogenesis there is a general correlation between the titer of rheumatoid factors and severity of the rheumatoid process. Patients with high titers have a much greater incidence of subcutaneous granulomatous nodules and a greater tendency toward erosive, crippling joint destruction than rheumatoid factor-negative patients. The occurrence of systemic vasculitis and visceral involvement with rheumatoid granulomata is virtually restricted to rheumatoid factor-positive patients, and is usually present in exceedingly high titers in such patients.

Antinuclear antibodies (ANA) have been reported in rheumatoid disease with an incidence of 10 to 60 percent, although generally in lower titer than in patients with systemic lupus erythematosus. There is a higher incidence of antinuclear antibodies in patients who are rheumatoid factor-positive. Accordingly, ANA-positive patients tend to have a higher incidence of erosive joint disease as well as vasculitic lesions, keratoconjunctivitis sicca, and Felty's syndrome. Davis has suggested that the ability of rheumatoid factor to react with antibody complexed with antigen affords a mechanism whereby a rheumatoid factor-positive patient might be protected from

systemic immune-complex disease. Thus the reaction of RF with complexed gamma globulin within the joint space would promote pagocytic removal, perhaps increasing local inflammation while sparing the individual from developing a more systemic immune complex disease. Others have found little clinical evidence that rheumatoid factor exerts a protective effect in patients with systemic lupus.

Studies of the serum complement system in RD have usually revealed normal to high values of total hemolytic complement, a common finding in inflammatory states in general, with the exception of systemic immune complex disease such as SLE and acute glomerulonephritis. A few severely and chronically ill patients with RD have been found to have low serum complement, however the implications of these findings are not clear at present. Synovial fluid complement levels in RD are substantially lower than in other inflammatory joint diseases.

Studies of complement components have suggested that the low synovial fluid values result from immunologic fixation, although the possibility of complement inhibitors has not been thoroughly studied. Again, these data imply the presence of complexed gamma globulin in the joint space.

The data currently available suggest that RD may result in part from a form of local immune-complex disease primarily involving the joints. Efforts in many laboratores are now being directed toward identifying the antigen which might be involved in such an immune complex. Because such an antigen should have the properties of persisting and disseminating in a given patient over many years, an infectious agent is being sought. Among the agents thus far implicated have been the Mycoplasma and certain Diphtheroid bacteria. These initially encouraging reports have not been convincingly reproducible, and a major thrust is now being made to implicate a slow or latent virus in the pathogenesis of this disease.

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* The concept of "latent viruses" discussed in detail by Docto. Phillips in this symposium pages 515-522.

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. . .In 1893 Buchner described how serum, which when fresh was able to kill certain bacteria, lost this ability after heating at 56°C. The heat-labile constituent which either had, or aided, this bactericidal action was called *alexine*. A more modern synonym is *complement*. Serum factors, which were active in the serum of guinea-pigs, immunized by heat-killed organisms, had been shown by Pfeiffer in 1894 actually to accomplish the dissolution of cholera vibrios. The bactericidal factor in this case proved to be specific for these organisms. A year later Bordet showed that the bacteriolytic and -cidal activity of an immune serum against cholera vibrios depended on two distinct factors: one was thermolabile and also present in normal serum (i.e. it resembled *alexine*), and the other was thermostable and specific (antibody).

From Humphrey JH, White RG: *Immunology for Students of Medicine, 2nd ed.* Philadelphia: F.A. Davis Company, 1964, page 7.

MYOPATHY IN THE COLLAGEN DISEASES*

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Among the several syndromes which are recognised under the heading of "collagen diseases", myopathy may be a dominant or minor feature. In this brief review an attempt will be made to outline the nature of the muscle disease which may occur in association with these illnesses, with accent on recent thoughts or developments. It is well to point out Pearson's cautionary note /1/ that pathological alterations may be found in muscle biopsies from patients with chronic diseases, and that these non-specific changes may contribute to the clinical muscle involvement.

Dermatomyositis and Polymyositis

Myopathy is the dominant feature of this syndrome group. Its incidence in the population is not known precisely although two estimates would suggest a rate of about five cases per million population per year. /2,3/ Approximately two-thirds of patients are female. In older patients an association with malignancy may exist. /4/ This association is not necessarily simultaneous and is one reason for the careful observation that these patients receive.

The clinical picture of patients with myositis is extremely variable and Pearson /5/ has characterised its extremes as (a) acute polymyositis with or without skin rash, severe constitutional symptoms and rapid and severe loss of strength, and (b) chronic myositis with gradual weakness evolving over several years, particularly in the limb girdle musculature.

Tenderness and induration of the muscles may be present, and biopsy may show a broad spectrum of changes with necrosis, degeneration of fibers, inflammatory infiltrates, regenerating fibers and fibrosis. This may be scattered and mild, or generalised and severe, and followed by profound muscle atrophy. Elevations of the serum activities of creatine phosphokinase,

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lactic dehydrogenase, glutamic oxalacetic transaminase and aldolase may be striking, particularly in acute patients and may be useful clinical guides. Recently myoglobin has been detected in serum and urine of patients with acute myositis. /6/ This heme-containing, oxygen-binding protein is normally found only in striated muscle and its appearance in the circulation and subsequent renal excretion is a specific manifestation of muscle injury or alteration. Approximately one-half of patients studied demonstrated myoglobinemia or myoglobinuria, and later unpublished findings indicate this ratio may be higher. Myoglobin was usually present in low concentration and often was present in serum and not urine, suggesting a renal threshold phenomenon. Myoglobinemia was most common among those patients with dermatomyositis, rather than polymyositis, and usually disappeared with institution of therapy. However, two patients in this group had persistent myoglobinemia and myoglobinuria and developed renal failure. This complication of myoglobinuric states /7-9/ should alert the physician to this rare but potentially catastrophic occurrence with severe myositis.

Attention has lately been focused on possible etiological factors which may play a role in inciting this illness. Autoimmune humoral factors (antimyosin, immunoconglutinin and antinuclear factors) were not found to be increased in incidence in a group of patients with polymyositis compared to patients with other muscle diseases. /10/ Similar negative findings for antimuscle antibodies have been reported. /11/ However, interest in the immunological determination of this illness is high because of its importance in the development of a laboratory model of this disease. Dawkins /12/ produced a generalized myositis in guinea pigs given injections of heterologous muscle mixed with Freund's adjuvant. These animals demonstrated delayed type hypersensitivity to heterologous and homologous muscle antigens. Kakulas /13/ has extended these observations by demonstrating that lymph node cells from sensitized animals could destroy tissue cultures of skeletal muscle cells. Currie and co-workers /14/ found in vito stimulation of lymphocytes from patients with polymyositis upon exposure to muscle antigens. In addition, lymphocytes from these patients appeared to bring about destruction of muscle cells in tissue culture after two to four days in most cases. In vito transformation of lymphocytes in response to autologous muscle in experimental myositis of guinea pigs has been noted. /15/

Theories of a possible viral etiology have been stimulated by the findings of intranuclear and cytoplasmic inclusions

resembling myxovirus particles in muscle cells by Chou. /16/ Inclusions in endothelial cells of muscle capillaries similar to those found in other collagen diseases have also been seen. /17/ However, attempts to identify myxovirus antigens in tissue, or to isolate virus from blood, muscle, or skin of patients have thus far been without reward. /18/

The meaning of these findings therefore is uncertain. Virus-like particles, or inclusions, have also been seen in several patients with other myopathic disorders /19,20/ as well as in patients with myositis accompanying herpes zoster. /21/

A word should be said about the association of myositis with malignancy in older patients because in these patients it is possible to envision that the same factor responsible for tumor development is also in some way related to development of myositis. Alternatively, the tumor itself may produce a myotoxic factor or lead to "auto-immune" processes which can attack muscle. At present there is no evidence to support these ideas, although in individual cases reappearance of tumor or development of second tumors associated with relapse of myositis strongly suggests a link in their etiologies.

The usual mode of therapy for affected patients has been with corticosteroids, although statistical data on results are difficult to interpret, and there are no prospective controlled trials. Spontaneous remissions occur and steroid effectiveness may be difficult to document. /22/ However, temporal remissions may be strikingly related to steroid therapy. For patients in whom this approach has failed, or with other contraindications, antimetabolite or immunosuppressive drugs have been used. Good results have been reported in a few patients treated with methotrexate /23/ and azathioprine. /24/

The initial response rate of treated patients may approach 75 percent and regeneration of damaged muscle does occur in this disorder. /25/

Scleroderma

Muscle disease marked chiefly by wasting and weakness may be a prominent feature of this illness. Biochemical and histological signs of a primary myopathy were found in the majority of 53 patients with progressive systemic sclerosis. /26/

Typically there was marked weakness of proximal muscles especially around the pectoral girdle, although wasting and weakness were commonly present in other muscle groups. Serum activity of creatine phosphokinase, lactic dehydrogenase and glutamic oxalacetic transaminase were generally normal, although elevations of lactic dehydrogenase were encountered at times. The average urinary creatine excretion was elevated, but decreased in some patients with time suggesting loss of muscle mass. Perivascular fibrosis was the chief histological finding in muscle samples.

In addition there may be other categories of patients with more active inflammatory change in muscle in association with scleroderma. These have been referred to under the term "sclerodermatomyositis". /27/ Nodular zones of interstitial inflammation have also been seen in muscle. /28/

Rheumatoid Arthritis

The patient with rheumatoid arthritis may manifest muscle weakness and loss of muscle volume. Muscle biopsy may reveal nodular lymphocytic infiltrates of variable size. This nodular myositis /29/ is commonly seen but is not specific for rheumatoid arthritis. /30/ In addition, an atrophic wasting of muscle also occurs. Myopathic changes occur in both proximal and distal muscle groups. In some patients vasculitis as well as nerve involvement may play a role in muscle fiber change. Histological changes in muscle occur in approximately one-half of patients with Sjögren's syndrome. /31/

Polyarteritis Nodosa

Although muscle weakness occurs in this disease, changes in muscle are usually secondary to vasculitis. The most common histological findings are inflammation adjacent to zones of necrotizing arteritis, areas of muscle necrosis or hemorrhage related to infarction, and atrophy associated with ischemic neuritis. Muscle biopsy is frequently a useful means of diagnosis, particularly if the muscle sampled is tender or clinically involved. Slightly over one-third of patients in a large series had positive muscle biopsies. /32/

Systemic Lupus Erythematosus

As in patients with rheumatoid arthritis, focal nodular collections of inflammatory cells may be found in the connective tissue of muscle, often near blood vessels. In addition "hydropic" vacuolation of small or large sections of muscle fibers can be seen. /33/ Lesions of this type have also been noted in patients with polymyositis. /5/ Although there are patients with marked weakness, clinical signs of myopathy generally are not prominent. In some patients, however, myoglobinemia as well as elevations of serum lactic dehydrogenase, creatine phosphokinase and glutamic oxalacetic transaminase are associated with muscle weakness in a situation suggestive of acute polymyositis.

Sarcoid

Symptomatic myopathy rarely occurs. Clinical muscle involvement was found in eleven of 800 patients reviewed. /34/ Asymptomatic muscle involvement, however, is considerably more common, and epithelioid granulomas in muscle may be detected by biopsy in about 50 percent of patients with sarcoidosis. These otherwise unsuspected findings seem especially frequent early in the disease, and are a useful means of diagnosis. Among patients with clinically apparent myopathy, palpable granulomatous nodules may be present, or there may be an acute myositis or chronic myopathy. In the latter instance, typical noncaseating granulomata may be associated with degeneration of muscle. Because of the paucity of reported cases, the full clinical picture is not well known; however, proximal muscles seem to be affected early, and there may be spontaneous remissions. Silverstein and Siltzbach /34/ have reviewed the literature and found reports of 21 patients with chronic sarcoid myopathy who were treated with corticosteroids. Twelve had objective improvement; nine did not. In the absence of other effective agents, they recommend treatment of these patients with corticosteroids.

Steroid Myopathy

Administration of steroid preparations may result in myopathic change in man and experimental animals. Cushing /36/

described severe weakness in patients with hypersecretion of adrenocortical hormones and many reports have appeared subsequently of steroid-related muscle weakness. Weakness usually begins insidiously, is most marked in proximal muscles, particularly of the lower extremities and is associated with muscle wasting. Reversal of this process can occur. Electron microscopic observation has revealed massive aggregates of glycogen in subsarcolemmal and intermyofibrillar sites /37/ as well as enlarged and degenerated mitochondria. /38,39/

In experimental animals, the pathological process seems divisible into an early phase marked by deposition of glycogen deposits, and a late phase characterized chiefly by necrosis of contractile elements, cellular infiltration, and phagocytosis. /40/ Mitochondrical change can be seen early in this process. It has been suggested that type II muscle fibers may be most vulnerable to steroid myopathy /41/ but this needs further study.

Distinction between steroid myopathy and a patient's previous disease which necessitated therapy is one of the most difficult and perplexing problems to which unfortunately there still exists no simple solution.

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Time and again it has been found that fresh blood serum has properties which are no longer present when the serum has been left to stand at room temperature for a day or two, or has been heated at 56°C for half an hour. It has already been mentioned that Bordet in 1898 first observed that rabbit antisera against sheep red cells, which when fresh would lyse the cells in high dilution, lost their haemolytic power on ageing or on being heated. He found, however, that the haemolytic activity was completely restored by adding fresh normal serum from several species of animal, but not by old or heated normal sera. This heat-labile activity present in normal serum was at the time named 'alexine' but is now termed 'complement'. Although complement activity is commonly tested for and measured in the same system that Bordet used, namely by its capacity to enable antiserum against sheep red cells (in practice antiserum against the Forssman antigen in the red cell surfaces) to cause haemolysis, there are many biologically important phenomena in immunology in which the same or a similar complement activity is involved. These include killing of bacteria by serum antibodies, opsonization, immune-adherance and conglutination, lysis of normal or of tumour cells by antibody against antigen on their surface, and the activation of serum by antigen-antibody complexes to produce 'anaphylatoxin'. It would clearly help our understanding of these phenomena if we knew what complement is and how it acts.

From Humphrey JH, White RG: *Immunology for Students of Medicine, 2nd ed.* Philadelphia: F.A. Davis Company, 1964. page 104.

JUVENILE RHEUMATOID ARTHRITIS

Jerry C. Jacobs, M.D.*

With an incidence of at least 1:25,000 children rheumatoid arthritis is one of the more common chronic disorders of early childhood. The most frequent year of onset in several series is between the first and second birthdays; more than half of the cases with onset in childhood start before the sixth birthday. Awareness of the frequency of this condition in early childhood leads to recognition of more cases, and avoids unnecessary and even harmful procedures.

SIGNS AND SYMPTOMS

The onset is usually insidious, with swelling of one or more joints, sometimes without complaints and without signs of systemic illness. About 20 percent of patients begin with swelling of a knee alone. Within a year most who will develop polyarthritis have done so. From a pediatrician's viewpoint trauma and infection are the most important diagnoses to think about in the 40 percent of patients with monarticular onset and joint fluid may be aspirated for examination and culture. Synovial biopsy has not been useful when the tuberculin skin test was negative and should be avoided as immobilization following surgery may result in unusual deformity.

A few children have fever as the sole presenting manifestation. The diagnosis may be suspected but cannot be made on this criteria alone although in this group the fever tends to be intermittent with daily spikes as high as 105-106 F and also daily recordings of 99 F. The children usually do not look as ill as youngsters with

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weeks of such high fever from other causes. Fortunately some of these youngesters develop a characteristic rash — salmon pink in color and evanescent, with individual spots coming and going almost as you watch. The rash tends to come out with temperature elevations, and may overlie joints. Occasionally it is pruritic. The experienced observer may make an earlier diagnosis by recognizing the exanthem.

Inflammation in the anterior chamber of the eye may be visible as cells and protein accumulation seen on slit lamp examination by an experienced ophthalmologist. Most rheumatoid children with uveitis do not have complaints or visible signs until late, after irreparable damage to the eyes has occurred. Therefore, slit lamp examination is part of the diagnostic evaluation and is repeated at regular intervals.

Cervical spine pain may be an early or presenting manifestation but radiological evidence of arthritis is not seen soon after onset.

Occasional patients have pericarditis as a part of their acute illness, and may have features of cardiac tamponade and congestive heart failure. Rheumatoid arthritis is one of the causes of idiopathic pericarditis in children, and may also occur without simultaneous clinical evidence of arthritis. It differes from the pericarditis seen in acute rheumatic fever — in these patients there is no evidence of concomitant valvular disease.

Classical rheumatoid nodules are rare in children and are almost invariably seen only in late severe cases. However, small transient nodules overlying extensor finger tendons are not uncommon, but are usually not seen early enough to aid a prompt diagnosis. The author and others have seen children referred for "rheumatoid nodules" without any other sign of disease. These children are usually brought to the doctor for asymptomatic subcutaneous masses noted on the extensor surfaces of the legs. Biopsy reveals pathology generally indistinguishable from a rheumatoid nodule. Such patients are not known to have ever developed any systemic disease and recognition of this syndrome is necessary to avoid repeated biopsies or harmful procedures and treatment. In one published case a child was subjected to auricular myocardial biopsy in an extensive search for evidence of rheumatic disease!

Morning stiffness or "gelling" is common but may have to be sought after by the physician as the parent may not be aware of it. An older sibling occasionally reports that the affected youngster crawls to the bathroom in the morning but is improved by the time mother arises. Tenosynovitis may accompany the arthritis and is occasionally mistaken for lymphangitis. As time goes on flexion contractures become a sine que non of the disease.

DIFFERENTIAL DIAGNOSIS

In youngsters presenting with migrating polyarthritis, rheumatic fever should be the admitting diagnosis. Rheumatoid arthritis is a chronic disease with definite diagnosis, in the absence of certain features already suggested, not possible until several weeks of persistent arthritis has been present. While patients may have brief, self-limited attacks before developing definite signs of disease, diagnostic accuracy is usually not obtainable for several weeks. The arthritis of rheumatic fever is generally gone by three weeks, provided recurrent episodes are not produced by recurrent administration and withdrawal of salicylates creating repeated "rebounds" which may be confusing.

Differential diagnosis requires careful consideration of a large number of other conditions. Systemic lupus, dermatomyositis, scleroderma and polyarteritis are always considered. Some of the other commonly confused disorders are listed below:

Osteomyelitis or septic arthritis treated with large doses of antibiotics for a brief period and then presenting as chronic swelling and pain in a joint. Pain in such patients may be out of proportion to the visible signs of arthritis. Radiological

evidence of osteomyelitis may not be seen for three months or more in such children. At the time of the original sepsis the bone or joint complaint was not noticed and a different diagnosis was made; the local sign disappeared at first and then more gradually recurred after treatment was withdrawn.

Acute leukemia with bone pain and joint effusions. Bone marrow aspiration may be necessary to make the diagnosis, and if steroids have been administered a remission may have been induced.

Ulcerative colitis and regional enteritis. Diarrhea may not be present or the history of diarrhea secreted or neglected. In children regional enteritis may result in high fever, arthritis, and growth failure without diarrhea.

Child abuse. Hitting the child across the fingers with a ruler may produce finger swelling suggestive of rheumatoid arthritis. While periostitis may be seen with early juvenile rheumatoid arthritis (JRA) flakes of bone broken off from the phalanges are diagnostic of trauma and involvement of fingers alone with persistent new bone formation is suspect. History of broken bones in such children, or feared baby sitters, may be clues.

Serum sickness-like reactions to medicines.

Hand-foot syndrome of sickle cell anemia.

Osteoid osteoma of the femur.

Gaucher's disease.

Familial Mediterranean fever.

Gonorrhea with arthritis.

Reaction to rubella vaccine.

Hysteria. This can produce joint complaints without objective signs of arthritis and characteristically with more disability in terms of school absence

or withdrawal from activities than is generally seen in proven rheumatoid children with similar complaints. Rarely a true rheumatoid adolescent will use the disease in similar fashion.

Anaphylactoid purpura. This is usually accompanied by a distinctive rash.

Hemophilia and other coagulation defects.

Hypertrophic osteroarthropathy. This is familial or secondary to lung or liver diseases.

Phosphate diabetes.

A number of other disorders may also be excluded including Reiter's syndrome, sarcoidosis, gout, agammaglobulinemia, Farber's disease, villonodular synovitis, and mucopolysaccharoidosis.

LABORATORY STUDIES

Anemia and elevated erythrocyte sedimentation rates commonly accompany severe disease. The anemia seems to result primarily from marrow inhibition and does not respond to iron, although elements of shortened red blood cell survival and increased gastrointestinal blood loss from medicines as well as iron and folate deficiency from poor nutrition may be demonstrated. Albumin is low in sick patients and gamma globulins high except in isolated patients with specific defects in gamma globulin synthesis. Rheumatoid factor is rarely present (10 percent) and then usually in severely affected patients in whom a diagnosis is easily established in its absence. The majority of children referred to us because of rheumatoid factor do not have it on our retest and their physicians have been misled so that the correct diagnosis is not made. In those in whom we do find rheumatoid factor only two-thirds have rheumatoid arthritis.

The early radiographic findings are joint effusions and juxta-articular demineralization. In young children with asymmetrical involvement growth centers on the involved side become more advanced after months of disease, and eventually that extremity or portion of it may be abnormally long. Signs of

erosions and joint destruction are late. Unusual, and so characteristic of JRA, are findings leading toward fusion at the C_2 - C_3 zygoapophyseal joints and at the temporomandibular joints.

Overall skeletal growth, however, is retarded by prolonged severe disease resulting in short stature. This has been demonstrated not to be due to growth hormone deficiency nor is it responsive to exogenous growth hormone, and so it is presumably a disease-induced cellular defect.

Diagnosis remains a clinical skill - always possible, if possible at all, without laboratory or radiographic aids. However, these ancillary studies are needed to exclude many conditions which may be mistaken for JRA.

The early literature tended to suggest a poor prognosis since interested clinics accumulated the most severely affected patients. It is generally accepted that about two-thirds of the children make a complete recovery and have no residual findings on examination after an average of two years of disease. About five percent of affected children die of either complications of the disease or complications of therapy. These include amyloidosis, Addisonian crises with stress following steroid withdrawal, overwhelming infections, rheumatoid cardiac nodules, and idiosyncratic reactions to drugs. Another five percent become severely handicapped, either limited to a bed-chair existence or blind as a result of uveitis. The other 25 percent of children include those with some residua of old but burnt-out disease and those whose disease remains intermittently active forever. On the whole, patients with severe systemic exacerbations followed by complete remissions do better than those with smouldering but continuously active disease.

TREATMENT

Most children respond well to aspirin given in doses of 100 mg/kg/24 hours divided between 6AM and 11PM if the children do not have high spiking fever and at four-hour intervals around the clock if they do. If the disease is adequately controlled by this regimen and no signs of salicylism appear, blood levels of salicylate are not obtained. If inadequate control is achieved after several weeks, blood levels are obtained

and dosage increased to the maximal tolerated amount. While we aim for a salicylate level around 25 mg/100 cc we have children completely controlled on less and others requiring and tolerating chronic levels as high as 48 mg/100 cc enough to be fatal in some other children. Parents and doctors must always be alert to signs of salicylism including tachypnea (sometimes mistaken for "croup" in these children), vomiting (called "gastroenteritis"), and depression with withdrawal to bed (the psychiatrist was called while additional aspirin was given to one of our poisoned youngsters). Educated parents are the best observers, and it is the physician's responsibility to teach the toxic signs at the time of prescribing the medicine. Medication is continued in our clinic until six months after all signs and symptoms of disease have disappeared.

The aim of treatment is to enable the child to lead a normal or almost normal life, attending school regularly in a regular class. If aspirin alone does not achieve this goal small doses of prednisone - 1.0 to 2.5 mg three times daily may be added, starting at the lower dose. More recently some of our more severe patients have received alternate day steroid therapy with 10 to 15 mg of prednisone every second morning as a single dose, plus their usual aspirin, with success.

In our own clinic we are not currently using gold or indomethacin because of fatalities which have occurred when our patients received them elsewhere. We recognize that others have better results with these agents than our statistics would support.

This statement also applies to surgical treatment with early synovectomy aimed at preventing joint deformity. Since two-thirds of our patients get completely well, a large multi-institutional study would be needed to document the value of such an approach. To date no such study has been performed and on the basis of the available evidence, we cannot recommend this procedure for general use in children.

Physical therapy to avoid or minimize progressive flexion contractures is helpful. The parents are taught the exercise program by one physician who sees all our patients. The parents conduct the program every day at home, and get reinforcement from our therapists. Night splints for the wrists are sometimes helpful and lifts on the heels of shorter legs help prevent contracture of the overgrowing knee. Later stapling may be needed at

the knee to avoid valgus deformities and overgrown legs.

Circular plaster and bed rest in our experience is harmful, requiring vigorous therapy to recover the losses of strength and muscle atrophy. The worst deformities we see are in new patients previously subjected to biopsy followed by circular plaster immobility.

Pericarditis, when present, is treated with large doses of systemic steroids for a few weeks, until it subsides. Uveitis is brought under control with steroid eye drops when possible. If complete control is not achieved with local therapy systemic steroids in moderately large doses are used for several weeks to achieve complete control, followed by an alternate day single dose regimen for maintenance so long as is necessary.

The most important factor in management is an optimistic attitude of a well-informed pediatrician whose goals are toward almost normal function of the child. Whenever a family member has a chronic disease, patients and their families become easily discouraged and, when depressed, maximize their disability and function poorly in all areas. Attention should be paid to how the child is doing in life situations, including peer and family relationships, and school. If there are additional handicaps besides arthritis an effort is made to be certain they also receive a maximum rehabilitative effort, including psychotherapy and, for teenagers, vocational guidance. While management thus requires a team approach the pediatric-rheumatologist, as coordinator of the team, has an opportunity to provide a kind of optimal comprehensive care.

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ANTINUCLEAR ANTIBODIES (ANA)

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The presence of antibodies directed against nuclei or components of nuclei has been recognized for many years. These antibodies have been found to react with whole nuclei, native and denatured DNA, soluble extract of nucleoprotein, histone, RNA and still other chemically undefined components of nuclei. Antinuclear antibodies (ANA) have been demonstrated by the use of a variety of techniques. These have included complement fixation, precipitation with nuclear antigens in agar, agglutination of latex or bentonite particles coated with DNA or nucleoprotein, ammonium sulphate precipitation of antibody with radioactive labelled DNA (Farr technique), and the indirect fluorescent antibody technique. /1,2/ Each of these methods has been used as a research tool. However, the technique most widely used as a routine laboratory procedure is the indirect fluorescent antibody technique. This procedure detects antibodies to all nuclear components and if one is specifically interested in detecting the antibody to native DNA, another method such as the Farr, complement fixation, or precipitation must be used with native DNA as the specific antigen.

METHODS FOR DETECTING ANA

The most sensitive technique for detection of antinuclear antibodies is the indirect fluorescent antibody technique. In this test, the patient's serum is allowed to incubate with a source of nuclei. All unbound antibody is washed off the slide. Then the slide is allowed to incubate with a fluorescein isothiocyanate labelled anti-human gamma globulin. This fluorescent anti-human gamma globulin reacts with any previously bound

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gamma globulin from the patient's serum. When viewed under ultraviolet light, the bound antibody has an apple green color. A variety of nuclear substrates has been employed. Since the antinuclear antibodies are not species specific, they will react with human tissue and with tissue from many animals as well as with bacterial, protozoal and viral DNA. /1/ The most commonly used substrates are mouse or rat liver and human peripheral buffy coat. The mouse or rat tissue is immediately frozen, sectioned on a cryostat and mounted on glass slides. It is preferable to use these tissue sections rather than human peripheral buffy coat because, as has been demonstrated, occasional sera stain granulocyte nuclei but do not react with tissue nuclei. /3/ This is particularly true of sera from some patients with rheumatoid arthritis. The data on the indirect fluorescent antibody test for ANA described below were obtained using mouse liver as substrate.

The Farr technique is also useful in detection of antibodies to DNA and seems to be more sensitive than complement fixation and much more sensitive than precipitation with DNA. /2/

ANA Use in Diagnosis

The indirect fluorescent antibody test is most valuable in ruling out the diagnosis of systemic lupus erythematosus (SLE). This test is positive using the patient's undiluted serum in all cases of clinically active SLE. The presence of ANA continues for prolonged periods after therapy although occasionally a patient in prolonged remission may have a negative ANA.

The indirect fluorescent antibody test for ANA should not be regarded as a specific diagnostic test for SLE. /4/ A positive ANA using undiluted sera is present in approximately 50 percent of patients with rheumatoid arthritis, 33 percent of patients with chronic discoid lupus erythematosus, 75 percent of patients with progressive systemic sclerosis, one quarter of patients with dermatomyositis and periarteritis nodosa. The test is usually positive in patients with chronic active hepatitis. In patients with juvenile rheumatoid arthritis, ANA is present in 73 percent of patients.

In addition to the above diseases, positive ANA may be present in asymptomatic patients receiving Pronestyl or isoniazid. /5,6/

CLINICAL SIGNIFICANCE OF ANTINUCLEAR ANTIBODIES

In Systemic Lupus Erythematosus

In acutely-ill patients with SLE, the pattern of nuclear fluorescence seen with the patient's undiluted serum is usually peripheral. /7/ The fluorescence is located on the rim or periphery of the nucleus with absence of fluorescence in the center. This pattern is due to antibodies directed against native DNA or against the DNA of the DNA-histone complex. /8/ Sera giving such a pattern possess complement-fixing antibodies to native DNA, bind more than 40 percent of radioactive DNA in the Farr technique and may also possess precipitating antibodies to native DNA. The titer of ANA in the indirect fluorescent antibody test is usually greater than 1:64 and may be as high as 1:1024 or greater.

As the patient is treated with corticosteroids and the clinical manifestations of the disease becomes suppressed, the pattern of nuclear fluorescence becomes diffuse. At this time, complement-fixing anti-DNA antibodies are no longer demonstrable. The binding of radioactive DNA using the Farr technique falls. In addition, the titer of ANA using the indirect fluorescent antibody technique gradually falls.

If an exacerbation of the disease occurs, the titer of ANA usually rises and the pattern may become peripheral.

In Rheumatoid Arthritis

The pattern of nuclear fluorescence in undiluted sera from patients with rheumatoid arthritis is usually diffuse. The titer is most frequently less than 1:16 but in some patients may range up to 1:512. Antibodies to native DNA are not present. The patients with positive ANA usually are those whose disease is most severe.

In Chronic Discoid Lupus Erythematosus

The pattern of nuclear fluorescence is either diffuse or may consist of fine discrete speckles throughout the nucleus. The titer is usually less than 1:16. These sera do not contain anti-DNA antibodies.

In Progressive Systemic Sclerosis

The pattern of nuclear fluorescence may be either diffuse or, more commonly, either fine or large speckles or nucleolar. Titers in this disease are in the same range as in SLE. However, in progressive systemic sclerosis, there is no correction between presence of ANA, type of pattern, or titer and the clinical activity of the disease. Similarly, there is no correlation between disease duration, system involved, or therapy and presence, titer or pattern of ANA. Sera from patients with progressive systemic sclerosis do not contain antibodies to DNA.

In Juvenile Rheumatoid Arthritis

Seventy-three percent of these patients have ANA using undiluted sera. The pattern is diffuse. Forty percent of patients have titers of greater than 1:16. These sera do not contain antibodies to DNA.

In Drug Induced ANA

Twenty percent of patients receiving isoniazid for tuberculosis have developed ANA from one to six months after the onset of therapy. /6/ These patients had no clinical evidence of SLE. Fifty percent of patients receiving Pronestyl developed antinuclear antibodies two to eighteen months after onset of therapy. /5/ In addition, symptoms of SLE developed in one-quarter of those developing ANA. In patients with clinical evidence of SLE after taking procainamide, a peripheral pattern may be present and high titers of ANA demonstrated, Antinuclear antibodies have also been found to be induced by oral contraceptives. /12/

INCIDENCE OF ANA IN THE NORMAL POPULATION

The incidence of ANA in the normal population is approximately two to four percent. However, in the aged population (60 years or older) the incidence of ANA has been reported to be 16 percent. /13/ These antibodies were found to be of the IgM and IgA classes in contrast to antibodies in SLE patients which are of IgG class in addition to IgM and IgA.

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CLINICAL ASPECTS OF SJÖGREN'S SYNDROME

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Sjögren's Syndrome, first clearly described in 1933, has assumed increasing importance in the field of arthritis during the past decade, largely following the clinical and pathological descriptions by the late Bunim and his associates in Bethesda./1,2/ While the major features of Sjögren's Syndrome (SS) are well known, a considerable amount remains to be defined more clearly. In particular, the prevalence of the disease, true incidence of the association with rheumatoid arthritis (RA) (how many clinics routinely perform a Schirmer's test on all their RA patients, for instance?) and the relationship of SS to the visceral complications of rheumatoid arthritis are all uncertain.

CLINICAL FEATURES

The full triad of SS consists of keratoconjunctivitis sicca (xerophthalmia - dry eyes), (xerostomia - dry mouth), and a connective tissue disorder (usually, but not exclusively, rheumatoid arthritis). The term "sicca syndrome" is reserved for cases in whom only the first two features are present.

Xerophthalmia

In most cases of SS, the diagnosis is simple. The commonest complaint in our experience has been "grittiness" or irritation of the eyes. The paucity of lacrimal secretion leads to corneal scarring and, sometimes, to corneal ulceration, vascularization and even perforation. The superficial abrasions can often be seen by shining a light from one side across the surface of the cornea. Schirmer's test, the Rose Bengal test and slit lamp examination are usually abnormal as well.

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Xerostomia

The dryness of the mouth may be sufficiently mild to pass unnoticed. There may be an unpleasant taste or dry throat. The patient may continually sip fluid, and a state resembling diabetes insipidus has been reported in this condition. Dental caries is widespread, and early. The healthy mouth normally contains a pool of saliva in the sublingual vestibule. This pool is often noticeably absent in SS.

Parotid enlargement occurs in approximately half the cases./3/ Rarely the submandibular and even the lacrimal glands may be obviously enlarged. One feature of SS is the sudden onset of sicca syndrome in some cases, sometimes with marked parotid enlargement. A history of "mumps" leading to the sicca syndrome is not infrequently obtained in patients with rheumatoid arthritis.

Connective Tissue Disorder

Rheumatoid arthritis is by far the most common third member of the triad, although systemic sclerosis, polyarteritis nodosa, and systemic lupus erythematosus (SLE) are well described. In the latter disease, it has been suggested that SS correlates with the nonerosive but deforming 'Jaccoud's' arthritis sometimes seen in SLE (Dubois, European Rheumatology Meeting, Brighton, 1971).

The RA is usually seropositive, nodular and moderately severe. Figures vary on the incidence of sicca syndrome in RA. Current opinion favors an incidence of 10 - 20 percent./4/ In our own experience with labial gland biopsy histological changes of SS were seen in 40 percent of patients with rheumatoid arthritis.* Using slit lamp examination following rose bengal staining, Lenoch and his colleagues /5/ found keratoconjunctivitis in no less than 58.4 percent of patients with RA. Clearly the incidence of SS in any series depends on the diagnostic methods used.

*Hughes GRV, Duckworth R, O'Riordan B: Unpublished observations.

PATHOLOGY

The salivary glands are infiltrated with lymphocytes and plasma cells, sometimes amounting to almost total diffuse replacement of the gland. True lymphoid follicles may be seen. The duct epithelium is hyperplastic and the acini atrophic. In a survey of 500 necropsies, moderate or severe grades of focal lymphocytic adenitis were present in 23 percent of females and nine percent of males. The more severe grades were concentrated in the age groups 35-64 in females, and as expected a highly significant association with RA was observed. In addition a moderate correlation with focal thyroiditis was found./6/

COMPLICATIONS AND ASSOCIATED CONDITIONS

Features of SS reported in the literature include alopecia, photophobia, intermittent pleurisy, peripheral neuropathy, bruising and generalized pruritus. While some of these features can readily be explained by the sicca syndrome, it is important to remember the ramifications of Sjögren's syndrome with other connective tissue disorders. For this reason 'complications' and 'associated disorders' are discussed together.

Parotitis

Superinfection, most frequently with Staphylococcus aureus, accounts for some cases of sudden enlargement of these glands in SS.

Respiratory Tract

The sicca syndrome extends down the tracheobronchial tree and hoarseness, recurrent laryngitis in RA are more likely to be due to this condition than to cricoarytenoid arthritis. In addition, recurrent pulmonary infections and atelectases are well-recognized. The relationship of the sicca syndrome to the more widespread pulmonary fibrosis of RA has not been studied.

Gastrointestinal Tract

While the pancreas may show the same histological changes as the salivary glands, acute and chronic pancreatis are rare. Gastric hyposecretion, as well as oesophageal dysphagia, is seen in SS /7/ as is achlorhydria.

Genitourinary System

Vaginitis sicca is occasionally troublesome and, while rarely volunteered as a symptom may be the first manifestation of SS. The kidney may be involved by SS, although at present little adequate documentation of this is available. A persistent renal defect in concentrating ability, first reported by Kahn et al /8/ may occur, a defect not reversible by vasopressen. Other tubular defects such as diffuse aminoaciduria are occasionally seen, although the degree to which hyperglobulinemia contributes to such defects remains to be clarified. In renal biopsies on eight patients with SS, renal lesions consistent with interstitial nephritis were present in six of the patients./9/ Comparable RA patients were not used as controls.

Reticulo-endothelial System

Leukopenia and splenomegaly are found more frequently in rheumatoid arthritis patients with sicca syndrome than in those without./4/ In 1964 Talal and Bunim /10/ reported the development of extrasalivary reticulum cell sarcoma (RES) in three of 58 patients with SS. The association of SS (and especially of patients with sicca syndrome alone) with neoplasms of the RES is now established, and provides an important link between connective tissue disorders and the reticuloses./11/

Others

A variety of other clinical features have been reported in association with SS, as discussed in the introduction. These include macroglobulinemia, vasculitis, Raynaud's syndrome /12/, non-thrombocytopaenic purpura, undue sensitivity to drugs /2/, peripheral neuropathy and myopathy./13/ The true incidence and importance of these features remains to be elucidated.

INVESTIGATIONS

Schirmer's Test

This simple test should be a standard procedure in all rheumatic disease patients. Its beauty lies in the "all or nothing" result usually obtained. A strip of blotting paper 5 x 35 mm (standard sterile Schirmer test papers are available) is hooked over the medial aspect of the lower eyelid and left for five minutes. In the normal eye, the irritation generally leads to soaking of the whole length of the paper. Less than 15 mm is considered abnormal.

Rose Bengal Staining

A drop of rose bengal or fluorescein dye is placed in the eye. This renders superficial scarring more easily visible. Ideally slit-lamp examination is then performed. While this is the most sensitive test for corneal scarring, its very sensitivity makes it less than specific for SS.

Labial Gland Biopsy

With the discovery that the pathological features of Sjögren's are mirrored in the small accessory salivary glands of the lower lip, labial gland biopsy became a useful diagnostic tool in SS./14/ These glands can often be felt as small pinhead sized lumps inside the lower lip. Under local anaesthetic, a small incision is made and the gland removed. In our own clinic, all SS patients biopsied have shown the histological changes described above, although up to 40 percent of our patients with RA have shown some degree of lymphoid infiltration.

Sialography

In SS, the ducts may show dilatation or sialectasis./15/ While claims have been made for the diagnostic specificty of the method, it has not achieved routine use in the diagnosis of SS.

^{99}Technetium (^{99}Tc) Scanning

^{99}Tc is selectively concentrated and excreted by the salivary glands. Autoradiography scanning methods have shown the principal site of ^{99}Tc transport (as well as of iodide) in the major salivary glands to be the epithelium of the intralobular ducts. ^{99}Tc scanning, while simple, has yet to prove its usefulness.

Other Tests

Serum hyperglobulinemia is frequent, and hyperviscosity syndrome may occur. Rheumatoid factors are generally present in some 75 percent of both SS and of sicca syndrome alone./3,12/ Positive LE cell tests and antinuclear factors are frequent. However, antibodies to DNA are not found in SS unless associated with SLE. The development of an immunoassay to measure these antibodies may help to clarify the diagnostic overlap between SLE and SS./16/

TREATMENT

Methylcellulose eye drops (1.0 percent) provide the most satisfactory symptomatic relief (and possibly protection) from xerophthalmia. However, a sizeable group of patients appear to obtain no relief from this therapy. The possibility of a super-infective conjunctivitis should be borne in mind if the symptoms become suddenly worse.

For the dry mouth, there is no universally acceptable sialogogue, although pure lemon juice is popular.

The treatment of the arthritis is not altered by the presence of Sjögren's. If the observation that these patients are more prone to drug hypersensitivity reactions is borne out, then caution will be needed, particularly in the use of phenylbutazone and gold.

COMMENT

This short review has concentrated on the clinical features of Sjögren's syndrome. It is emphasized that this is a condition as yet incompletely defined and far from fully recognized. Only with better appreciation of the true frequency of the condition, will its relationship to other disorders and to malignant lymphoma formation be appreciated.

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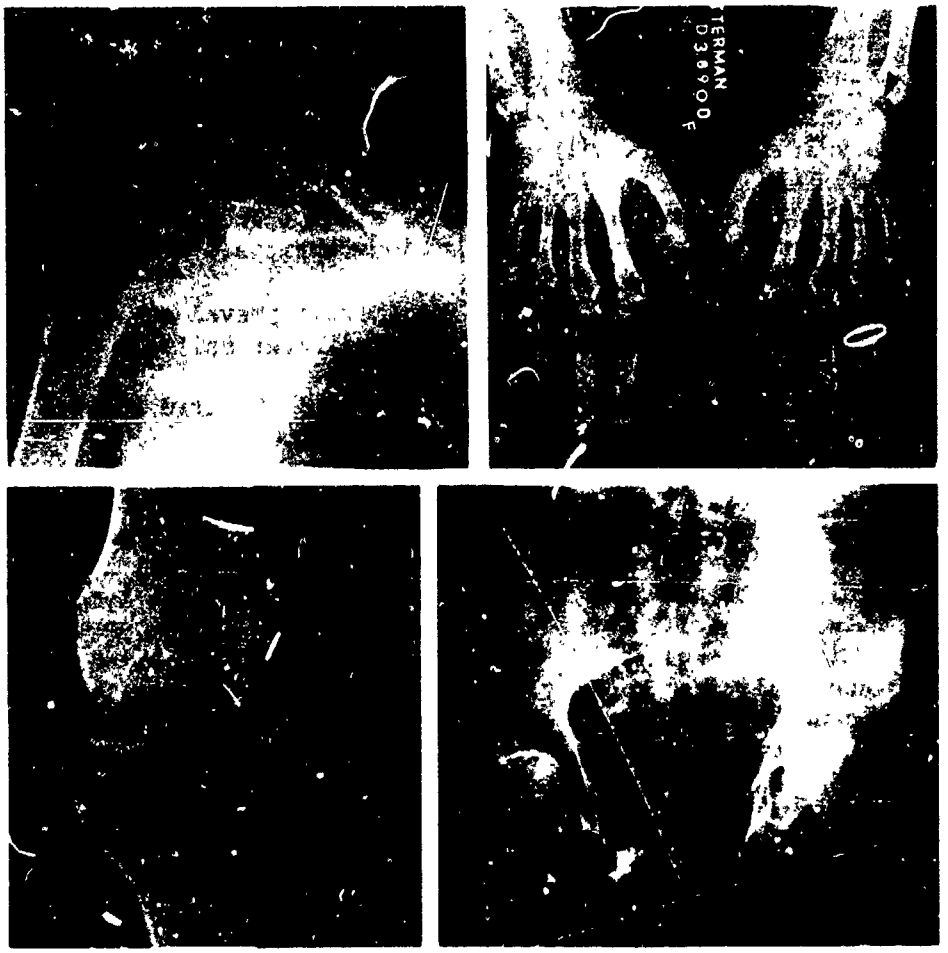

CHONDROCALCINOSIS

PSEUDOGOUT*

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Pseudogout (calcium pyrophosphate dihydrate crystal deposition disease), is a common recurrent arthritis whose unique radiologic and laboratory characteristics make it, when considered in differential diagnosis, one of the most easily identifiable arthridites. As a form of crystal synovitis it is a model for a mechanism of inflammatory joint disease. This paper briefly outlines the clinical and laboratory characteristics of this disease and reviews present concepts of the pathogenesis of crystal synovitis.

Clinical Characteristics. Epidemiology and Incidence.

Most commonly this disease is seen in the middle-aged to elderly of both sexes, men slightly more than women, whites slightly more than blacks. In large series, the average age of patients is 72 years, the usual range 50-100 years, but patients 20 years old have been reported, although most cases are sporadic, strong familial instances of the disease have been known.

The exact incidence of clinical attacks of pseudogout is unknown; radiologic findings characteristic of the disease are found in seven percent of elderly persons. Patients with hyperparathyroidism, hemachromatosis, diabetes, hypertension, uremia, and urate (true) gout are prone to have concomitant pseudogout. Some measure of the general frequency of pseudogout is available in the following statistic: over the past year, two percent of consultation requests to the rheumatic disease service of the Hospital for Special Surgery have been for pseudogout, compared to four percent for urate gout.

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Diagnosis

The clinical course and radiographs may suggest the diagnosis, but synovial fluid analysis, which must demonstrate crystals, is necessary to confirm the diagnosis.

Pathogenesis

Although the crystals consist of calcium pyrophosphate dihydrate (CPPD), expressed as $CaP_2O_7 \cdot 2H_2O$, serum and urine inorganic pyrophosphate levels are normal. Synovial fluid levels are high. The mechanism of precipitation of crystals within the synovial fluid space is unknown; but low levels of synovial fluid alkaline phosphatase have been suggested as a contributing factor. Once in the synovial fluid as crystal, CPPD probably activates Hageman factor and the kinin and complement system, releasing chemotactic complement components which attract PMNs. The PMNs ingest the crystals. Phagocytic release of chemotactic lysosomal enzymes presumably increases chemotactic activity of the synovial fluid, attracting more PMNs, completing the cycle of inflammation and leading to a clinical attack of arthritis. Differences between clinical episodes of gout and pseudogout may relate to lower chemotactic activity and lower (intracellular) membranolytic activity of CPPD crystals compared to urate crystals.

Therapy

Therapeutic efforts are aimed at halting the local cycle of inflammation. In some cases aspiration of the involved joint is adequate to provide relief. More often additional anti-inflammatory therapy is indicated. Most commonly used regimens are phenylbutazone (800 mg for one day, 600 mg for two days, and 400 mg for the next one to three days), intra-articular corticosteroid, or indomethacin (200-400 mg per day). Colchicine is not routinely effective. With proper management an attack can be aborted within a day or two. Unlike urate gout, pseudogout has no universally recognized prophylaxis against recurrent attacks.

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Clinical Course

Three types of attacks are recognized: acute (the most common), subacute, and chronic. Acute attacks are generally monoarticular; chronic tend to be polyarticular. The onset of an acute attack is moderately abrupt, onset to peak pain of 12-36 hours, compared to 4-18 hours for urate gout. An attack frequently occurs a few days following hospitalization for an acute medical illness such as myocardial infarction or pneumonia. Duration of an untreated acute attack is a few days to a few weeks, but the chronic form can be disabling for months to years.

The most frequently involved joints are the knees, followed in order by the hands, ankles, feet, shoulders, and hips. Podagra is rare. Fever up to 103 F is seen. The joints are seldom as intensely inflammed as they are in urate gout; peeling skin as the attack subsides is unusual.

Laboratory Findings

The white blood cell count (WBC) is normal to moderately elevated and the erythrocyte sedimentation rate moderately elevated. Blood chemistry may reveal a concomitant hyperglycemia, hyperuricemia or hypercalcemia when associated diseases are present. Synovial fluid analysis reveals a cloudy fluid with good mucin clot; synovial WBC counts are 1000 to 50,000 cu mm, with a predominance of polymorphonuclear leukocytes (PMNs). Polarized light microscopy demonstrates short, rhomboid crystals both intra and extracellularly. The crystals are weakly positively birefringent and are thus distinguishable from the usually needle-shaped negatively birefringent urate crystals, which are also found in ten percent of cases of pseudogout. (Care must be taken not to confuse CPPD crystals with calcium oxalate crystals when this substance has been used as an anticoagulant.)

Radiographic studies show linear calcification in hyaline cartilage about the knees, wrists, pubis, hips, shoulders, and other joints, and in the knee menisci. Accelerated degenerative changes may be seen as well.

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CRYOPATHIES

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The purpose of this paper is to present information that is now available, particularly from an immunologic and rheumatologic prospective, on circulating "cold precipitable" proteins. Initial emphasis will be placed on general information, with specific consideration being given later to each topic as warranted by its importance in clinical medicine.

Historical Prospective

It was not until 1947 that Lerner and Watson /1/ summarized the world's extant literature on "protein that precipitated spontaneously from cooled serum". They suggested that the term "cryoglobulin" be used to describe this unique property, and added their case to the nine others already in existence. Proper homage was paid to Wintrobe and Buell /2/ for their initial description of a "cryoglobulin" in a patient with far advanced multiple myeloma. The authors' insight in describing this protein abnormality did not extend into properly defining its nature. By several laboratory determinations (solubility, ultraviolet spectrophotometry, nitrogen content) they thought these proteins resembled globulinc, but consideration of molecular weight and viscosity seemed tc make it unlikely. The authors believed these proteins were manufactured in the liver, despite the evidence that five of the original nine patients mentioned in the world's literature up to that time had multiple myeloma, a known plasma cell malignancy even then. Final clarification of the nature and source of these cryoglobulins was to be accomplished in succeeding years by other investigators. /3,4/

In 1957 Smith and Von Korff /5/ reported on a cold induced "heparin precipitable fraction" of human plasma and tried to relate the presence of this protein to several disease states. Initial investigation proved this "fraction" to be in large

measure a fibrinogen like polymer and because of its cold requirement for production, was called a "cryofibrinogen".

By 1943, Wasserman and State /6/ had summarized a number of diseases that had as a concomitant abnormality the presence of an antibody that agglutinated a wide variety of homologous and heterologous erythrocytes at 0 to 5C. The term "cold agglutinin" was used to describe this protein.

Finally in the pre-antibiotic era when syphilis and its complications provided enough case material for a complete subspecialty practice, from 10 to 15 percent of patients with "syphilitic infections of some chronicity" developed a cold induced syndrome characterized by Raynaud's phenomenon, abdominal cramps, fever, bronchial asthma, hemoglobinuria, tachycardia, anemia, and hypotension. /7/ As the basic underlying abnormality seemed to be an erythrocyte antibody whose expression was temperature-dependent, the term "cold hemolysin syndrome" was introduced.

Four temperature-dependent protein abnormalities were thus defined three were globulins, the fourth a fibrin-like precursor. All had the inherent ability to cause Raynaud's phenomenon, or acrocyanosis, and in some instances both.

The rather frequent finding of these particular entities in rheumatology make it imperative that the differential diagnosis be immediately accessible.

CRYOGLOBULINS (Cryoglobulinemia)

Cryoglobulinemia is often but not invariably associated with a cold-induced clinical syndrome that manifests itself with a variety of signs and symptoms. TABLE I.

While the greatest number of reported cases of cryoglobulinemia are secondary to either multiple myeloma or macroglobulinemia, the association of cryoglobulin with a growing number of disease states exists. TABLE II. Essential cryoglobulinemia is a diagnosis only infrequently made and can be considered only after all secondary forms have been excluded.

TABLE I

SIGNS AND SYMPTOMS OF CRYOGLOBULINEMIA

Cyanosis	Urticaria /10/	Gangrene /12/
Numbness /8/	Purpura /11/	Vasculitis /14/
Raynaud's /9/	Vascular occlusion /12/	Glomerulonephritis /14/

TABLE II

DISORDERS IN WHICH CRYOGLOBULINS HAVE BEEN REPORTED /15/

Myeloma and macroglobulinemia	Hemolytic anemia
Chronic lymphatic leukemia and lymphoma	Subacute bacterial endocarditis
Polyarteritis nodosa	Leprosy
Cirrhosis	Syphilis
Reticulosis	Infectious mononucleosis
Sarcoidosis	Cytomegalovirus mononucleosis
Systemic lupus erythematosus	Acute glomerulonephritis
Rheumatoid arthritis	"Essential" cryoglobulinemia
Ankylosing spondylitis	Kala-Azar
Sjogren's syndrome	Polycythemia rubra vera

The detection of cryoglobulin is straightforward. Freshly drawn blood is allowed to clot at 37C following which the serum is separated and placed in a 0-4C environment for 24 to 48 hours. The amount of cryoglobulin can be qualitatively graded as 1+ (minimal) to 4+ (maximal) or quantitatively measured by optical density readings following suspension in warm saline.

Because the phenomenon of cryoprecipitability depends on no special reagents, the abnormal protein is discovered frequently by a laboratory technician who happens to leave a serum sample in a refrigerator overnight. Alternatively, the first indication of the presence of a cryoprotein may be marked difficulty in drawing a patient's blood with a syringe at room temperature or marked rouleau noted on a peripheral blood smear.

The development within the past three decades of extremely sophisticated laboratory procedures (immune protein electrophoresis, immune diffusion, immunofluorescence, ultra centrifugation) has resulted in detailed investigation of cryoglobulins.

Cryoglobulins are γ globulins of the IgG, IgM, "mixed" IgG-IgM /13/ or IgG-IgA /16/ classes. Molecular weights range from 60,000 to greater than 1,000,000. Svedburg ultracentrifuge density coefficients range from 3.5S /17/ to 19S.

Normally macroglobulins (19S) that combine with 7S globulins (i.e., macroglobulins with "rheumatoid factor" activity) produce a 22S peak on ultracentrifugation. In cases of "mixed cryoglobulinemia" (19S globulins that complex with 7S globulins to form a cryoglobulin) however, this 22S peak does not occur. The IgM-IgG complex separates into 19S and 7S peaks respectively. Interestingly, if the 19S and 7S peaks found in the mixed cryoglobulins are analyzed independent of one another, frequently neither fraction alone may have the ability to cryoprecipate and only upon recombination will the precipitate form. /13/ The explanation for this observation is presently lacking.

Recently Stastney and Ziff /18/ studied a group of patients with systemic lupus erythematosus (SLE) who had demonstrated elevated cryoglobulins in their sera. Several of the patient's sera, when subjected to ultracentrifugation, demonstrated an 11S peak in addition to the expected 7S and 19S peaks. This 11S peak thus far had been characterized as the first protein fragment in the first component of complement ($C1_q$). Of the patients with demonstrated cryoglobulins (11 of 31), 10 of the 11 (91 percent) had decreased levels of the third component of complement (C3), whereas in 25 SLE patients without demonstrable cryoglobulins only three (12 percent) had decreased C3 levels. (C3 presently is the most commonly measured fraction in studies of complement utilization).

Meltzer and Franklin /13/ studied 11 patients with "mixed cryoglobulinemia". Three of their patients died of acute renal failure. At postmortem these patients had histologic evidence of diffuse proliferative glomerulonephritis. Prior to their demise these same patients were noted to have low or absent levels of complement. Immunofluorescent studies done on these kidneys demonstrated the presence of C3 within the glomerular tufts.

These two divergent lines of investigation have both pointed to the impressive interrelationship of cryoglobulins and complement. It is within reason to speculate that the IgG-IgM "mixed" cryoglobulin in Meltzer's three patients dying of diffuse glomerulonephritis circulated as an "immune complex"

that had the ability to activate the complement system (in a manner analogous to the "immune complex" of lupus glomerulonephritis recently reviewed by Christian /19/). Why the remaining eight survivors did not develop renal dysfunction, however remains obscure.

While extremely important potentially, the findings of Stastney and Ziff /18/ demand independent verification and, more pointedly, explanation. Most assuredly not all lupus patients with decreased serum complement levels have elevated cryoglobulins, but the finding of cryoglobulins in a patient with SLE may be an early indicator of pending complement utilization and hence an acceptable criteria for early treatment. Christian /20/ noted that all (12 of 12) SLE patients with cryoglobulins, had "signs of active SLE".

Meltzer and Franklin /13/ studied the stability of the cryoglobulin molecule in their 1966 paper. The cryoglobulins retained their cryoprecipitability after being heated at 56C for 30 minutes (thereby demonstrating the function of cryoprecipitability to be independent of complement utilization). They reprecipitated greater than 50 times without loss of activity following redissolution at 37C, and finally seemed not to lose their precipitability following storage at 0C for greater than four years.

The mechanism underlying cryoprecipitation is presently unknown. Cryoglobulins have thus far proved to be structurally indistinguishable from "normal" circulating immunoglobulins. Furthermore, it is unknown by what precise means cryoglobulins exert their symptomatology. Although the cryoglobulin concentration is a major factor in predicting the presence of symptoms, it does not seem to be the main factor. Many patients with cryoglobulin levels as high as 1.5 to 1.8 gm/100 cc are asymptomatic whereas others with as little as 0.1 to 0.6 gm/100 cc do have symptoms directly attributable to the cryoprotein. /13/

If the cryoglobulin concentration should exceed 2.0 gm/100 cc /13/ then symptoms do almost invariably occur, but it becomes impossible to separate symptoms due to hyperviscosity from those of cryoglobulinemia.

CRYOFIBRINOGEN

Heparinized plasma taken from healthy individuals will develop when cooled at 4C for 18 hours up to 0.27 gm/100 cc of a gelatinous, flocculent material. /5/ Amounts greater than this have been shown to be associated with a number of disease states. TABLE III.

TABLE III

CONDITIONS ASSOCIATED WITH CRYOFIBRINOGEN /21/

Acute rheumatic fever
Rheumatoid arthritis
Bacterial infection
Neoplastic disease
Uveitis
Pregnancy
Idiopathic

Investigational data have defined this material as a "fibrinogen like" polymer loosely associated with heparin. The material has a similar electrophoretic mobility as fibrinogen, similar sedimentation characteristics, is clottable, and is not found in serum. It has been shown that several other proteins are present but their exact nature is presently undefined.

The initial enthusiasm generated by the discovery of this precipitate has not been sustained when it has been shown that there is no correlation between circulating cryofibrinogen, regardless of its concentration, and specific symptomatology. In two patients with the malignant form of systemic lupus erythematosus and periarteritis /21/ cryofibrinogen levels were found to be below the predicted range in spite of high fevers, extremely high sedimentation rates, and elevated "C" reactive protein. The observation of widespread vascular fibrinoid lesions at postmortem examination in these two cases lead to the hypothesis that the low cryofibrinogen level was a manifestation of its supra-normal consumption. The lack of reproducibility, however, in similar diseases with widespread fibrinoid lesions (and conversely its extremely high concentration in diseases where no immunologic, histologic or

vasculitic process could be defined) has tended to minimize the importance of this finding. /22/

The general concensus now is that cryofibrinogen is no more sensitive or informative than other "acute phase" indicators (e.g., erythrocyte sedimentation rate, "C" reactive protein) and in many cases is actually less sensitive. A case report /22/ describing a patient with a pulmonary malignancy, multiple thromboses, and an elevated cryofibrinogen level is available, but when one reads this report he finds no evidence that the cryofibrinogen was causally related to the thromboses. Cryofibrinogen must, at present time, be considered investigative and further studies will have to be completed before its true importance can be established.

COLD AGGLUTININ SYNDROME

Of the patients who will be seen medically for symptoms and signs consistent with Raynaud's and acrocyanosis, the majority will prove to be the idiopathic (Raynaud's disease) or an early manifestation of an evolving collagen disease.

There are, however, a small number of cases whose symptoms can be traced to the presence of an abnormal 19S circulating macroglobulin which has the ability to agglutinate erythrocytes in a suitable environment. /23/

This cold agglutinin can be found in normal individuals with a titer range from 1:2 to 1:128. /24/ Transient acute titer elevations are seen in viral infections, mycoplasma infections, mononucleosis, bronchiectasis and many influenza like diseases. Generally high sustained titers can be seen in "lymphoproliferative" disorders. /25/

There remains a group, generally elderly people, who present with the triad of acrocyanosis (resembling Raynaud's), hemolytic anemia, and hemoglobinuria. It is not unusual to find cold agglutinin titers of 1:1,000,000 and above in these patients. /26/ Titers of this magnitude can result in massive hemolysis, peripheral thrombosis, and are potentially fatal.

It has been shown that the temperature at which cold agglutinins become clinically manifest is a direct function of

its titer. Symptoms and signs arising from acute and subacute titer elevations will rarely occur if the patient is not exposed to temperature below 20C. Idiopathic cold agglutinin disease, however, with the extremely high titers mentioned above can cause erythrocyte agglutination and hemolysis at temperatures as high as 30-33C, the normal temperature of the skin. /27/ It is in this group that spontaneous necrosis of fingertips, fingers, ears, toes, and feet have been described. /28/ Whereas the agglutinating property of this immune globulin is independent of complement, the hemolytic potential is not realized without complement utilization.* /29/

Digital pain, which is almost a universal occurrence in all but the earliest forms of Raynaud's, is absent in the acrocyanosis caused by cold agglutinins. The reason for this is not understood.

There is one office procedure which may immediately direct your attention to the possibility of cold agglutinins in the patient with cyanotic hands have him immerse just one finger in a warm water sink. The patient suffering from cold agglutinin syndrome will show a rapid resolution of the cyanosis in that finger alone. The patient with Raynaud's will demonstrate complete resolution of all cyanosis or no change following the same procedure.

COLD HEMOLYSIN SYNDROME

The discovery of antispirochetal antibiotics has virtually eliminated the cold hemolysin syndrome from present day clinical medicine. Case studies will infrequently appear in the literature that are not related to long standing syphilis, but they are exceedingly rare. /26/

This entity is extremely interesting because of the bithermic potential of the IgM antibody. Unlike the cold agglutinin syndrome where antibody attachment to the erythrocyte surface and the expression of the antibody presence (agglutination or hemolysis) occur at the same low temperature (20C),

*The role of complement in cold agglutinin disease is described in Doctor Cohen's paper on pages 523-536 of this symposium.

the antibody of this cold hemolysin syndrome attaches to the red cell receptor site in a temperature range that causes no signs or symptoms, and that only after exposure to warmer environments (> 25C) will hemolysis occur.

COMMENT

In addition to the foregoing process, there are several other conditions associated with cold intolerance causing Raynaud's like symptoms. TABLE IV. These conditions are not, however, immunologically mediated and consequently outside the scope of this paper. Reference will be cited in the bibliography directing the reader to specific papers discussing these conditions.

TABLE IV

OTHER CONDITIONS ASSOCIATED WITH COLD INTOLERANCE /26/

Raynaud's disease /31/
Ergotism and heavy metal intoxication /30/
Shoulder girdle compression /32/
Occupational disorders (pneumatic hammer disease, typists, pianists) /31/
Myxedema /34/

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